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(54) Quinindolinone derivatives, process and intermediates for their preparation and pharmaceutical compositions containing them.

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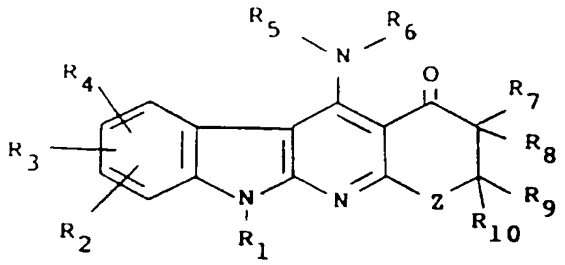
Description

This invention relates to novel compounds having pharmacological activity, to a process for their preparation, to compositions containing them and to their use in the treatment of mammals.

EP-A-0249301 (Beecham Group p.l.c.) describes pyrido[2,3-b]indoles which are useful in the treatment of CNS disorders.

A class of compounds has been discovered, which compounds have been found to have CNS activity, in particular anxiolytic and/or anti-depressant activity.

Accordingly, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R_1 is hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-4} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl;

R_2, R_3 and R_4 are independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, C_{1-6}alkylthio, hydroxy, C_{2-7} alkanoyl, chloro, fluoro, trifluoromethyl, nitro, amino optionally substituted by one or two C_{1-6} alkyl groups or by C_{2-7} alkanoyl, cyano, carbamoyl and carboxy, and phenyl, phenyl C_{1-4} alkyl or phenyl C_{1-4} alkoxy in which any phenyl moiety is optionally substituted by any of these groups;

R_5 and R_6 are independently selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-4} alkyl, C_{2-6} alkenyl, C_{1-7} alkanoyl, C_{1-6} alkylsulphonyl, di-(C_{1-6} alkyl)amino C_{1-6} alkyl, 3-oxobutyl, 3-hydroxybutyl, and phenyl, phenyl C_{1-4} alkyl, benzoyl, phenyl C_{2-7} alkanoyl or benzenesulphonyl any of which phenyl moieties are optionally substituted by one or two halogen, C_{1-6} alkyl, C_{1-6} alkoxy, CF_3, amino or carboxy, or R_5 and R_6 together are C_{2-6} polymethylene optionally interrupted by oxygen or NR_{11} wherein R_{11} is hydrogen or C_{1-6} alkyl optionally substituted by hydroxy;

R_7, R_8, R_9 and R_{10} are independently selected from hydrogen, C_{1-8} alkyl optionally substituted by one or two hydroxy, oxo, C_{1-4} alkoxy, halogen or CF_3 groups, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-4} alkyl, C_{2-7} alkanoyl, C_{2-6} alkenyl or C_{2-6} alkynyl either being optionally substituted by one, two or three halogen atoms or C_{1-4} alkyl, C_{3-7} cycloalkenyl optionally substituted by one or two halogen or C_{1-4} alkyl groups, C_{3-7} cycloalkenyl-C_{1-4} alkyl in which the cycloalkenyl ring is optionally substituted by one or two halogen or C_{1-4} alkyl groups, and phenyl optionally substituted by one or two halogen, C_{1-6} alkyl, C_{1-6} alkoxy, CF_3, amino or carboxy,

or R_7 and R_8 together and/or R_9 and R_{10} together are C_{3-6} polymethylene optionally substituted by C_{1-6} alkylor C_{2-6} alkenyl; and

Z is $(CR_{14}R_{15})_n$ where n is 0, 1 or 2 and R_{14} and R_{15} are independently selected from hydrogen, C_{1-6} alkyl or C_{2-6} alkenyl.

Unless otherwise specified alkyl groups including those in alkoxy, alkenyl and alkynyl moieties within the variables R_1 to R_{15} are preferably C_{1-6} alkyl, more preferably C_{1-3} alkyl, such as methyl, ethyl, n- and iso- propyl, and may be straight chain or branched. The term halogen includes fluorine, chlorine, bromine and iodine.

It will be appreciated in selecting variables R_1, R_5 and R_6 that the relevant nitrogen atom is not directly attached to an unsaturated carbon atom.

Values for R_1 include hydrogen, methyl, ethyl, n- and iso-propyl, n-, iso-, sec- and tert-butyl, n-, sec-, iso- and neo-pentyl, prop-2-enyl, prop-2-ynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclopropyl- C_{1-4} alkyl, cyclobutyl-C_{1-4} alkyl and cyclopentyl-C_{1-4} alkyl where values for C_{1-4} alkyl include methylene and ethylene. Preferably R_1 is hydrogen, methyl, ethyl, propyl or prop-2-enyl, most preferably methyl.

Values for R_2, R_3 and R_4 include hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, hydroxy, chloro or phenyl C_{1-4} alkoxy. Preferably, two of R_2, R_3 and R_4 represent hydrogen, and more preferably R_2, R_3 and R_4 each represent hydrogen.

Values for R^5 and R^6 include hydrogen, methyl, ethyl, n- and iso- propyl, n-, sec-, iso- and tert-butyl, n-, sec, iso- and neo-pentyl,cyclopentyl, cyclohexyl, cycloheptyl, cyclopentyl-C_{1-4} alkyl, cyclohexyl-C_{1-4} alkyl and cycloheptyl-C_{1-4} alkyl, where values for C_{1-4} alkyl include methylene and ethylene, but-2-enyl, but-3-enyl,1-methylprop-2-enyl, formyl, acetyl, propionyl, methylsulphonyl, 3-dimethylaminobutyl, 3-oxobutyl, 3-hydroxybutyl, phenyl, benzyl, benzoyl, benzylcarbonyl and benzenesulphonyl, or R_5 and R_6 together form C_4 or C_5 polymethylene, $-(CH_2)_2-O-(CH_2)_2-$ or $-(CH_2)_2-NR_{11}-(CH_2)_2-$ where R_{11} is preferably methyl.

Preferably R_5 is hydrogen and R_6 is hydrogen or C_{1-6} alkyl. More preferably R_5 and R_6 are hydrogen.

Values for R_7 and R_8 include hydrogen, methyl, ethyl, n- and iso-propyl, n-, iso-, sec- and tert-butyl, each alkyl moiety being optionally substituted by hydroxy, oxo, C_{1-4} alkoxy or CF_3, halogeno-C_{1-4} alkyl, particularly mono- or dihalogeno-C_{1-4} alkyl where the halogen atoms are chlorine or fluorine, prop-2-enyl, prop-2-ynyl, but-2-enyl, but-3-enyl, but-2-ynyl and but-3-ynyl, each alkenyl or alkynyl moiety being optionally substituted by one to three halogen atoms, particularly one or two chlorine atoms or C_{1-4} alkyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, cyclopropy-C_{1-4} alkyl, cyclobutyl-C_{1-4} alkyl, cyclopentyl-C_{1-4} alkyl and cyclohexyl-C_{1-4} alkyl, cyclopentenyl, cyclohexenyl, cyclopentenyl-C_{1-4} alkyl and cyclohexenyl-C_{1-4} alkyl, each cycloalkenyl moiety being optionally substituted by one or two halogen or C_{1-4} alkyl groups, or phenyl,

or R_7 and R_8 together form C_4 or C_5 polymethylene optionally substituted by C_{1-6} alkyl or C_{2-6} alkenyl.

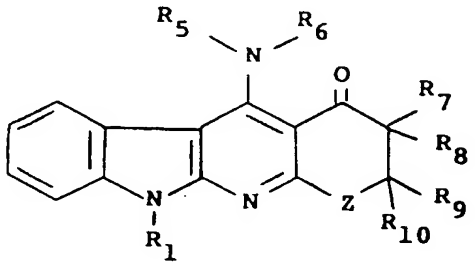
Preferably R_7 is hydrogen, C_{1-6} alkyl or C_{2-6} alkynyl and R_8 is hydrogen or C_{1-6} alkyl. More preferably R_7 is hydrogen, methyl or ethyl and R_8 is hydrogen or methyl.

Values for R_9 and R_{10} include those listed above for R_7 and R_8, in particular hydrogen, methyl, ethyl, n- and iso-propyl, n-, iso-, sec- and t-butyl, prop-2-enyl, but-3-enyl and phenyl. Preferably R_9 is hydrogen or methyl and R_{10} is hydrogen, methyl or phenyl.

Where n is one or two, values for R_{14} and R_{15} include hydrogen, methyl, ethyl, n- and iso- propyl, n-, iso-, sec- and t-butyl, prop-2-enyl and but-3-enyl. Preferably R_{14} is hydrogen and R_{15} is hydrogen or methyl. More preferably R_{14} and R_{15} are hydrogen.

Preferably n is 1 or 2. More preferably n is 1.

There is a favoured group of compounds within formula (I) of formula (II) or a pharmaceutically acceptable salt thereof:

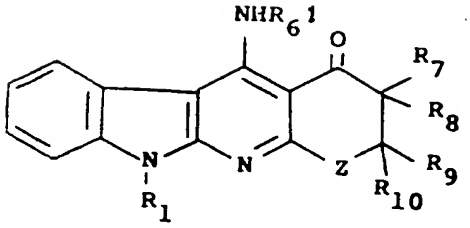


(II)

wherein R_1, R_5, R_6, R_7, R_8, R_9, and Z are as defined in formula (I).

Preferred values for R_1, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{14} and R_{15} are as described under formula (I).

There is a preferred group of compounds within formula (II) of formula (III) or a pharmaceutically acceptable salt thereof:



(III)

wherein R_6^1 is hydrogen or C_{1-6} alkyl and R_1, R_7, R_8, R_9, R_{10} and Z are as defined in formula (I).

Preferred values for R_1, R_7, R_8, R_9, R_{10}, R_{14} and R_{15} are as described for the corresponding variables in formula (I).

R_6^1 is preferably hydrogen.

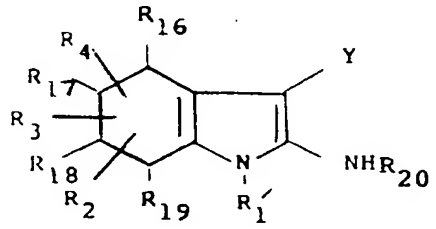
The compounds of the formula (I) can form acid addition salts with acids, such as the conventional pharmaceutically acceptable acids, for example, maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulphonic.

It will be appreciated that the compounds of formula (I) in which R_1, R_5 or R_6 is hydrogen may exist tautomerically in more than one form. The invention extends to each of these forms and to mixtures thereof.

Compounds of the formula (I) may exist in the form of optical and geometric isomers. The present invention comprises all such optical and geometric isomers and mixtures thereof including racemates.

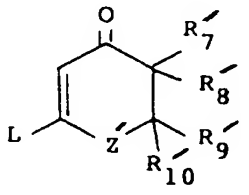
Compounds of formula (I) may also form solvates such as hydrates, and the invention also extends to these forms. When referred to herein, it is understood that the term "compound of formula (I)" also includes solvates thereof.

The present invention also provides a process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, which process comprises the condensation of a compound of formula (IV):



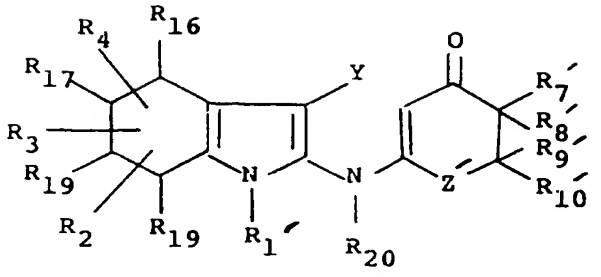
(IV)

with a compound of formula (V):



(V)

wherein R_1' is R_1 as defined in formula (I) or an N-protecting group, R_2, R_3 and R_4 are as defined in formula (I), R_{16}, R_{17}, R_{18} and R_{19} are each hydrogen or R_{16} and R_{17}, and R_{18} and R_{19} together represent a bond, L is a leaving group, Y is a group CN or COL_1, where L_1 is a leaving group, R_{20} is hydrogen or an N-protecting group and R_7', R_8', R_9', R_{10}' and Z' are R_7, R_8, R_9, R_{10} and Z respectively, as defined in formula (I) or a group convertible to R_7, R_8, R_9, R_{10} and Z, respectively, to give an acyclic enamine intermediate of formula (VI):



(VI)

wherein Y, R_1', R_2, R_3, R_4, R_{16}, R_{17}, R_{18}, R_{19} and R_{20} are as defined in formula (IV) and R_7', R_8', R_9', R_{10}' and Z' are as defined in formula (V); and thereafter, optionally or as necessary, and in any appropriate order, cyclising the enamine intermediate, separating any enantiomers, converting R_{20} when hydrogen to an N-protecting group, converting R_7', R_8', R_9', R_{10}' and Z' to R_7, R_8, R_9, R_{10} and Z, respectively, when Y is a group COL_1, converting the resulting hydroxy group to a leaving group and reacting the latter with a compound HNR_5R_6, removing any R_1' N-protecting group, removing any R_{20} N-protecting group, converting R_{16}, R_{17}, R_{18} and R_{19} when hydrogen to two bonds, interconverting R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10} or Z and/or forming a pharmaceutically acceptable salt of the compound of formula (I).

Suitable examples of the leaving group L include halogens, such as chloro and bromo, hydroxy, C_{1-6} acyloxy such as acetoxy or C_{1-6} alkoxy, such as methoxy or ethoxy, preferably hydroxy. When L is hydroxy, it will be appreciated that the compound of formula (V) exists in more than one tautomeric form.

Intermediates of formula (VI), and salts thereof which can be optionally isolated before cyclisation, are novel and form an aspect of this invention.

The condensation step may be carried out under conditions conventional for condensation reactions, at elevated temperatures in an inert solvent such as toluene or benzene in the presence of a catalyst such as para-toluene-sulphonic acid, with water separation.

The cyclisation of the enamine intermediate of formula (VI) may also be carried out under conventional conditions, in the presence of a strong base such as an alkali metal alkoxide, for example sodium methoxide in a suitable solvent such as methanol, at elevated temperature, or in the presence of a Lewis acid such as zinc chloride, copper (I) acetate or tin (IV) chloride in a suitable solvent such as n-butyl acetate at elevated temperatures. Lewis acid catalysed cyclisation using copper (I) acetate or tin (IV) chloride is preferred.

It should be appreciated that for the cyclisation of a compound of formula (VI) R_{20} is preferably hydrogen.

Conversion of R_{16}, R_{17}, R_{18} and R_{19} when hydrogen to two bonds may be carried out under conventional aromatisation conditions, with an oxidising agent such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, in an inert solvent such as benzene or toluene.

Alternatively, the conversion may be carried out by catalytic dehydrogenation using a conventional metal catalyst such as Pd/C in a suitable solvent such as xylene or mesitylene at elevated temperature, for example 100° - 180°C, or by sulphur dehydrogenation under conventional conditions.

In the compound of formula (IV), it is preferred that R_{16} and R_{17}, and R_{18} and R_{19} together represent a bond.

Suitable examples of R_1' N-protecting groups include benzyl, mono- or di-methoxybenzyl, which may be removed conventionally, for example by heating with $AlCl_3$ in benzene, or by treatment with trifluoroacetic acid and anisole, optionally in the presence of sulphuric acid and optionally with heating.

Conversion of R_1 hydrogen to R_1 alkyl, alkenyl or alkynyl may be carried out by treatment of the NH compound with a strong base, such as sodium hydride in dimethyl formamide, followed by reaction with the appropriate alkyl, alkenyl or alkynyl halide, preferably the iodide or bromide.

Suitable examples of a leaving group L_1 when Y is COL_1, include hydroxy and alkoxy, such as ethoxy or methoxy, more preferably methoxy. In such cases the reaction of the compounds of formulae (IV) and (V) gives a resulting compound having an hydroxy group in, the 4-position of the pyridine ring. The hydroxy group may be converted to a leaving group such as those defined above for L, preferably halo such as chloro, by reaction with a halogenating agent such as phosphorus oxychloride or phosphorus oxybromide. The leaving group may be displaced by the compound HNR_5R_6 under conventional conditions for nucleophilic aromatic displacements, at elevated temperatures in an inert solvent such as toluene, methanol,

ethanol, pyridine, dimethyl formamide or dioxan. Alternatively, the reaction may be carried out in neat HNR_5R_6 which functions as the solvent.

Conversion of R_5 and R_6 hydrogen to other R_5/R_6 may be carried out in accordance with conventional procedures for the alkylation or acylation of a primary amine. Acylation may be carried out by reaction with the appropriate acyl halide. However, R_5/R_6 other than hydrogen or acyl groups are preferably introduced via the route in which Y is COL_1 in the compound of formula (IV), by displacement of the leaving group with the compound HNR_5R_6 as discussed above.

Interconversion of R_2, R_3 and R_4 may be carried out by conventional procedures for the conversion of aromatic substituents. Thus, for example, a chloro substituent may be introduced by direct chlorination using standard conditions, such as chlorine in chloroform.

Examples of group Z' include $(CR_{14}'R_{15}')_n$ where n is as previously defined and R_{14}' and R_{15}' are R_{14} and R_{15} or groups convertible thereto.

Conversions of R_7', R_8' and R_{14}' and R_{15}' in Z' (n in Z' is 1 or 2), wherein R_7', R_8', R_{14}' and R_{15}' are R_7, R_8, R_{14} and R_{15} respectively, as defined in formula (I) or groups convertible thereto, may be carried out by the reaction of a corresponding compound wherein R_7', R_8', R_{14}' or R_{15}' is hydrogen with two equivalents of lithium diisopropylamide mono (tetrahydrofuran) at low temperatures in a suitable solvent such as tetrahydrofuran. The resulting enolate anion is treated with a molar equivalent of an R_7'-, R_8'-, R_{14}'-or R_{15}'-halogen compound, as desired, for example iodomethane or iodoethane, to give the corresponding compound in which R_7' and/or R_8' and/or R_{14}' and/or R_{15}' is other than hydrogen. The procedure may be repeated to achieve disubstitution.

Reaction of the enolate anion with an α,ω-dihaloalkane may be carried out to give the corresponding compound of formula (I) in which R_7 and R_8 together are polymethylene, as described by G. Stork et al., J. Amer. Chem. Soc., 1973, 95, 3414-5.

It should be appreciated that where the conversion is carried out on a compound of formula (VI), it may be necessary in some circumstances to have R_{20} as a N-protecting group to prevent reaction of the R_7'-, R_8'-, R_{14}'-, or R_{15}'- halogen compound with the secondary amine function and also to direct substitution to Z.

Suitable examples of R_{20} N-protecting groups include trimethylsilyl and 2-(trimethylsilyl)ethoxymethyl, which may be removed conventionally, for example using t-butylammonium fluoride in an inert solvent.

If R_7', and R_8' are hydrogen and preferential conversion of R_{14}' and R_{15}' is desired, it is necessary to first of all protect R_7' and R_8'. An example of a suitable protecting group is trimethylsilyl.

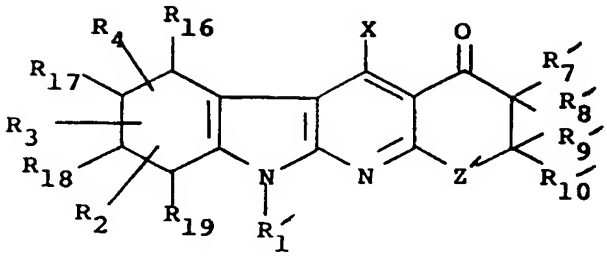
Preferential conversion of R_{14}' and R_{15}' in Z' (n in Z' is 1 or 2) in compounds of formula (VI) may alternatively be carried out as described by P.S. Mariano et al J. Org. Chem. 1981, 46, 4643-54, by reacting a compound of formula (VI) in which R_{14}' and R_{15}' are hydrogen with 2 moles of potassium or lithium bis-(trimethylsilyl)amide at low temperatures in an inert solvent such as tetrahydrofuran. The resulting £-enolate anion is treated as described above to introduce the required groups R_{14}' and R_{15}'.

An example of a group R_7', R_8' R_9', R_{10}', R_{14}' or R_{15}' convertible to R_7, R_8, R_9, R_{10}, R_{14} or R_{15} respectively, is an alkylthiomethyl group, which can afford R_7, R_8, R_9, R_{10}, R_{14} or R_{15} respectively, as a methyl group by reductive desulphurisation, for example using Raney Nickel. Separation into enantiomers maybe carried out, if desired, by first oxidising the alkylthiomethyl group to the chiral sulphoxide as described by H.B. Kagan et al., J. Amer. Chem. Soc. 1984, 106, 8188 or H.B. Kagan et al., Nouv. J. Chim. 1985, 9, 1, followed by physical separation of the diastereoisomers (for example by fractional crystallisation or chromatography). Reductive desulphurisation will afford the single enantiomer.

Conversions of R_9' and R_{10}' hydrogen when n in Z is O may be carried out by a procedure analogous to that described above for R_{14}' and R_{15}'.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or derivative.

A class of intermediates obtained by the reaction of certain compounds of formula (IV) with certain compounds of formula (V) comprises compounds of formula (VII) or a salt, thereof:

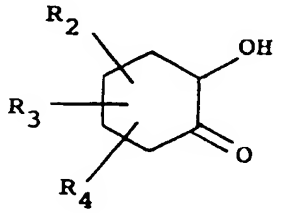


(VII)

wherein X is NH_2, OH or chloro, R_1', R_2, R_3, R_4, R_{16}, R_{17}, R_{18} and R_{19} are as defined in formula (IV), and R_7', R_8', R_9', R_{10}' and Z' are as defined in formula (V) with the proviso that when R_1', R_7', R_8', R_9', R_{10}', and Z' are R_1, R_7, R_8, R_9, R_{10} and Z as defined in formula (I) and R_{16} and R_{17}, and R_{18} and R_{19} together represent a bond, X is not NH_2.

Intermediates of formula (VII) are novel and form an aspect of this invention.

Compounds of formulae (IV) and (V) are known or can be prepared by analogous processes to those used for preparing known compounds. Thus, for example, the compounds of formula (IV) where R_{16}, R_{17}, R_{18} and R_{19} are each hydrogen may be prepared by the reaction of a compound of formula (VIII):



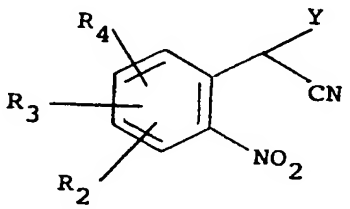
(VIII)

with $CH_2(CN)_2$ and an alkylamine such as methylamine or an aralkylamine such as 4-methoxybenzylamine or benzylamine by a procedure analogous to that described by H.J.Roth et al., Arch.Pharmaz., 1975, 308, 179.

Alternatively, the compound of formula (VIII) may be reacted with $NCCH_2CO_2C(CH_3)_3$ and an alkylamine such as methylamine or an aralkylamine such as benzylamine by a procedure analogous to that described by H.J.Roth et al., Arch.Pharmaz., 1975, 308, 179. This gives a compound of formula (IV) in which Y is COL_1 and L_1 is t-butoxy, which may be converted to other L_1 by conventional procedures.

Compounds of formula (IV) where R_{16}, R_{17}, R_{18} and R_{19} together form two bonds may be prepared by procedures conventional in indole chemistry.

Thus, for example, a compound of formula (IX):



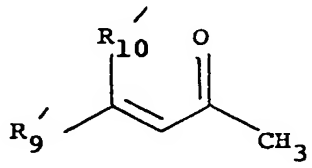
(IX)

wherein R_2, R_3 and R_4 are as defined in formula (I) and Y is as defined in formula (IV), may be reduced and cyclised by treatment with a metal such as zinc, iron or tin in an acid such as acetic acid, in an inert solvent such as toluene at elevated temperature by a procedure analogous to that described by K.L.Munshi et al J.Het.Chem. 1977, 14, 1145. Alternatively, when Y is CN the reduction and cyclisation may be effected by

treatment with aqueous sodium dithionite by a procedure analogous to that described in EP 0107963 (Example 1). This procedure gives a compound of formula (IV) in which R_1' is hydrogen and which may be N-substituted under conventional conditions as described above to give other compounds of formula (IV).

Compounds of formula (IX) are known or may be prepared by procedures analogous to those for preparing known compounds.

Compounds of the formula (V) where R_7' and R_8' are hydrogen, Z' is a methylene radical and L is hydroxy may be prepared by reaction of a compound of formula (X):



(X)

with a malonic ester compound, for example dimethyl - or diethylmalonate, followed by cyclisation, hydrolysis and decarboxylation. Compounds of the formula (X) may be prepared by known methods, for example by reaction of a saturated aliphatic aldehyde with acetone at elevated temperatures in the presence of an acid or basic catalyst.

The above procedure may be adapted to give compounds of the formula (V) where R_7' is other than hydrogen by use of a malonic ester compound in which the methylene radical is substituted by R_7', where R_7' is other than hydrogen.

Alternatively, compounds of formula (V) in which L is hydroxy, for example optionally substituted 1,3-cyclopentanediones, 1,3-cyclohexanediones and 1,3-cycloheptanediones may be prepared via epoxidation of the corresponding cyclopent-2-en-1-one, cyclohex-2-en-1-one and cyclohept-2-en-1-one compounds with hydrogen peroxide under basic conditions as described in Organic Synthesis, Coll. Vol. (IV), 552-3, (1963), and subsequent ring opening using catalytic quantities of tetrakis-(triphenylphosphine)palladium(O) and 1,2-bis(diphenylphosphino)ethane as described in J. Amer. Chem. Soc. 1980, 102, 2095-6.

Compounds of formula (V) in which L is hydroxy or C_{1-6} alkoxy, R_7' and/or R_8' are other than hydrogen and R_9', R_{10}' and Z' are as defined for formula (V) may be prepared from compounds of formula (V) in which L is hydroxy and R_7' and/or R_8' are hydrogen as described by G. Stork et al., J. Org. Chem., (1973) 38, 1775-6. Treatment with a C_{1-6} alkyl alcohol to give an intermediate in which L is C_{1-6} alkoxy is followed by reaction with an equivalent of lithium diisopropylamide mono (tetrahydrofuran) at low temperatures in a suitable solvent such as tetrahydrofuran. The resulting enolate anion is treated with a molar equivalent of an R_7'- or R_8'-halogen compound or with an α,ω-dihaloalkane by an analogous procedure to that described above for the conversion of R_7' and R_8' in the process of the invention, including separation into enantiomers, if desired. The procedure may be repeated to achieve disubstitution. Where Z' is a bond, simultaneous interconversion of R_7' or R_8' hydrogen and R_9' or R_{10}' hydrogen may be achieved by treatment with two equivalents of lithium di-isopropylamide and subsequent reaction with excess halogen derivative as described by M. Koreeda et al., J. Chem. Soc. Chemical Communications, (1979) 449-50. Conversion to L hydroxy may be effected by acid hydrolysis.

Alternatively, compounds of formula (V) in which L is hydroxy and R_7', R_8', R_9', R_{10}' and Z' are as defined for formula (V), may be prepared by the reaction of an ester of an α-β unsaturated carboxylic acid with a substituted or unsubstituted propan-2-one as disclosed in GB 1485610 (Hoechst).

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, is usually adapted for oral or parenteral administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, or injectable or infusable solutions or suspensions. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tableting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for pharmaceutical use. By pharmaceutical use is meant for use as an active therapeutic substance in the treatment or prophylaxis of disorders in mammals including humans. Compounds of formula (I) and their pharmaceutically acceptable salts are of particular use in the treatment of CNS disorders, in particular anxiety or depression.

The invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of CNS disorders, in particular anxiety or depression in mammals including humans.

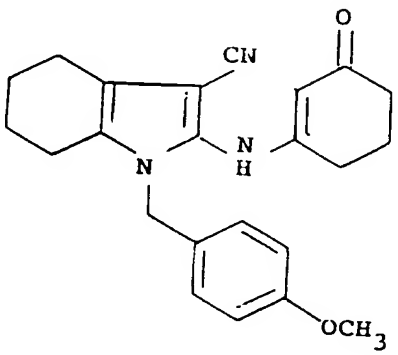
The dose of the compound used in the treatment of CNS disorders, such as anxiety or depression will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20.0 mg, for example 0.2 to 10 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.01 to 100 mg/kg; and such therapy may extend for a number of weeks or months.

Within the above indicated dosage range, no adverse toxicological effects are indicated with the compounds of the invention.

The following Examples illustrate the preparation of the compounds of the invention. The following Descriptions illustrate the preparation of intermediates to the compounds of the present invention.

Description 1

1-(4-Methoxyphenyl)methyl-2-[(3-oxo-1-cyclohexen-1-yl)amino]-4,5,6,7-tetrahydro-1H-indole-3-carbonitrile (D1)

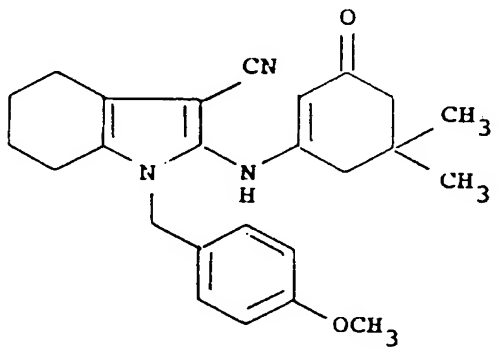


(D1)

A solution of 2-amino-1-(4-methoxyphenyl)methyl-4,5,6,7- tetrahydro-1H-indole-3-carbonitrile (prepared by the method described in EP-0249301A, Description 5) (22.4g; 79.7mM), 1,3-cyclohexanedione (9.3g; 79.7mM) and para toluenesulphonic acid (2g; 10.5mM) in toluene (350ml) was vigorously refluxed with distillation until no more water distilled over (ca. 1h). The solution was cooled and poured onto water (500ml). The toluene layer was separated, and the aqueous layer extracted with dichloromethane (x2). The combined organic phase was washed with saturated aqueous sodium hydrogen carbonate, dried (Na_2SO_4) and evaporated to dryness to afford a pale yellow solid. Crystallisation from ethyl acetate afforded the title compound (D1)(24.7g; 82%) as a pale yellow solid.
m.p. 143-5°
NMR ($CDCl_3$) δ:
1.70-1.88 (4H, m), 1.92-2.10 (2H, m), 2.25-2.45 (6H, m), 2.45-2.60 (2H, m), 3.80 (3H, S), 4.78 (2H, s), 5.06 (1H, s), 6.15 (1H, broad s), 6.78-6.96 (4H, m).

Description 2

2-[(5,5-Dimethyl-3-oxo-1-cyclohexen-1-yl)amino]-1-(4-methoxyphenyl)methyl-4,5,6,7-tetrahydro-1H-indole-3-carbonitrile (D2)

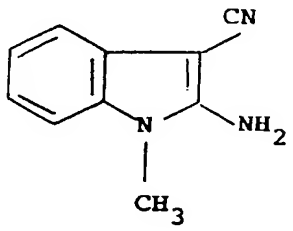


(D2)

The title compound (D2) was prepared from 5,5-dimethyl-1,3-cyclohexanedione in 78% yield using a procedure similar to that described in Description 1. Product was obtained as a buff coloured solid.
NMR ($CDCl_3$) δ:
1.06 (6H, s), 1.66-1.87 (4H, m), 2.18 (2H, s), 2.24 (2H, s), 2.30-2.45 (2H, m), 2.45-2.60 (2H, m), 3.78 (3H, s), 4.77 (2H, s), 5.05 (1H, s), 6.08 (1H, broad s), 6.77-6.95 (4H, m).

Description 3

2-Amino-1-methyl-1H-indole-3-carbonitrile (D3)



(D3)

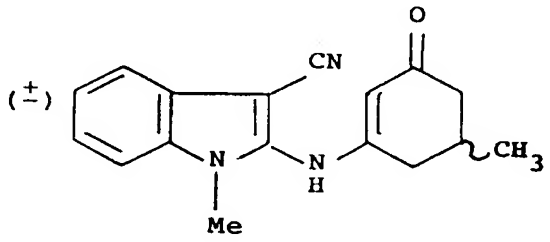
To a solution of 2-amino-1H-indole-3-carbonitrile (produced by a method analogous to that disclosed in EP 0107963 example 1) (20.0g 12.7mM) in DMF (100ml) at ca. 5° and under an atmosphere of nitrogen, was added potassium tert-butoxide (14.59g, 12.7mmol) portionwise over 5 minutes. The cooling bath was removed and the whole stirred at room temperature for 30 minutes. The whole was then recooled and methyl iodide (8ml, 12.7mM), dissolved in DMF (20ml), added dropwise such that the temperature remained below 5°. After a further 40 minutes at this temperature, water (500ml) was added dropwise and the resulting solid collected by filtration, washed with water and dried under reduced pressure to give the title compound (D3) (13.08g, 60%) as a brown solid.

NMR (D_6 DMSO) δ:

3.63 (3H, s), 7.00-7.20 (4H, m), 7.21-7.40 (2H, m).

Description 4

(±) 2-[(5-Methyl-3-oxo-1-cyclohexen-1-yl)amino]-1-methyl-1H-indole-3-carbonitrile (D4)



(D4)

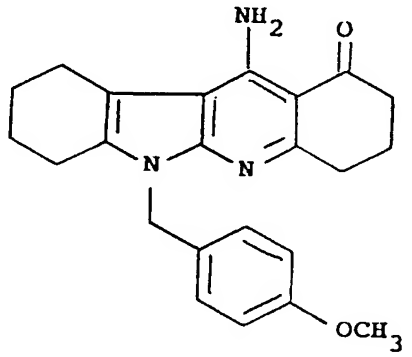
The title compound (D4) was prepared from intermediate D3 and 5-methyl-1,3-cyclohexanedione in 69% yield using a procedure similar to that described in Description 1. Product was obtained as a pale yellow solid. m.p. 235-6°.

NMR (D_6 DMSO) δ:

1.29 (3H, d, J = 7.5Hz), 2.04-2.84 (5H, m), 3.78 (3H, s), 4.99 (1H, s), 7.30-7.55 (2H, m), 7.64-7.85 (2H, m).

Description 5

11-Amino-6-(4-methoxyphenyl)methyl-1,2,3,4,7,8,9,10-octahydro-6H-quinindolin-1-one (D5)



(D5)

Method A

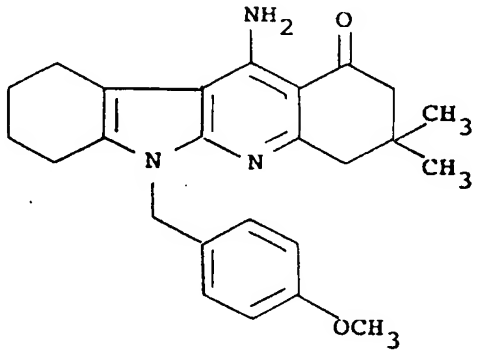
A suspension of intermediate D1 (0.5g; 1.33mM) copper (1) acetate (0.043g; 0.33mM) in n-butyl acetate (10ml) was heated to reflux whereupon a solution resulted. After refluxing for 10 minutes, the whole was cooled and poured onto 5M ammonium hydroxide solution (20ml). The whole was shaken with dichloromethane (20ml), the organic layer separated, and the aqueous layer further extracted with dichloromethane (x2). The combined organic phase was washed with water and brine, dried (Na_2SO_4) and evaporated to afford a crude solid (0.5g). Crystallisation from methanol gave the title compound (D5) (0.40g; 80%) as a pale yellow solid.
m.p. 146-7°.
NMR ($CDCl_3$) δ:
1.70-1.90 (4H, m), 2.00-2.17 (2H, m), 2.40-2.53 (2H, m), 2.59-2.70 (2H, m), 2.82-2.96 (2H, m), 2.96-3.09 (2H, m), 3.78 (3H, s), 5.26 (2H, s), 6.80 (2H, d, J = 8Hz), 7.05 (2H, d, J = 8Hz).

Method B

A solution of 2-amino-1-(4-methoxyphenyl)methyl-4,5,6,7-tetrahydro-1H-indole-3-carbonitrile (prepared by the method described in EP-0249301A, Description 5) (20.0g; 71mM), 1,3-cyclohexanedione (8.3g; 71mM) and para toluenesulphonic acid (0.5g; 2.6mM) in toluene (280ml) was vigorously refluxed with distillation until no more water distilled over. The solution was cooled and n-butyl acetate (280ml) and tin (IV) chloride (0.83ml; 7.1mM) were added. The solution was then refluxed for 10 minutes and allowed to cool. The reaction mixture was poured onto 1% aqueous sodium hydroxide solution (500ml) and shaken with dichloromethane (200ml). The organic layer was separated, and the aqueous layer further extracted with dichloromethane (x2). The combined organic phase was washed with water and brine, dried (Na_2SO_4) and evaporated to dryness to afford a crude solid. The crude solid was flash chromatographed on t.l.c. alumina with dichloromethane elution, followed by crystallisation from methanol to give the title compound (D5) (21.2g; 79%) as a pale yellow solid in two crops.
m.p. 146.5-7°.
NMR ($CDCl_3$) δ:
1.70-1.90 (4H, m), 2.00-2.17 (2H, m), 2.40-2.53 (2H, m), 2.59-2.70 (2H, m), 2.82-2.96 (2H, m), 2.96-3.09 (2H, m), 3.78 (3H, s), 5.26 (2H, s), 6.80 (2H, d, J = 8Hz), 7.05 (2H, d, J = 8Hz).

Description 6

11-Amino-3,3-dimethyl-6-(4-methoxyphenyl)methyl-1,2,3,4,7,8,9,10-octahydro-6H-quinindolin-1-one (D6)

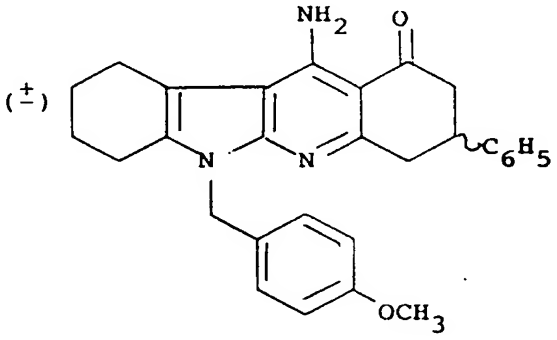


(D6)

A suspension of intermediate D2 (10.0g; 24.8mM) tin (IV) chloride (0.3ml, 2.48mM) in n-butyl acetate (100ml) was heated to reflux. After refluxing for 10 minutes, the whole was cooled and poured onto 2.5M sodium hydroxide solution (200ml). The whole was shaken with dichloromethane (200ml), the organic layer separated, and the aqueous layer further extracted with dichloromethane (x2). The combined organic phase was washed with water and brine, dried (Na_2SO_4) and evaporated to afford a crude solid (10.0g). Crystallisation from methanol gave the title compound (D6) (9.29g; 93%) as an off-white solid.
NMR ($CDCl_3$) δ:
1.10 (6H, s), 1.65-1.92 (4H, m), 2.32-2.59 (4H, m), 2.89 (4H, s), 3.75 (3H, s), 5.27 (2H, s), 6.70-6.90 (2H, m), 6.96-7.13 (2H, m).

Description 7

(±) 11-Amino-6-(4-methoxyphenyl)methyl-1,2,3,4,7,8,9,10-octahydro-3-phenyl-6H-quinindolin-1-one (D7)

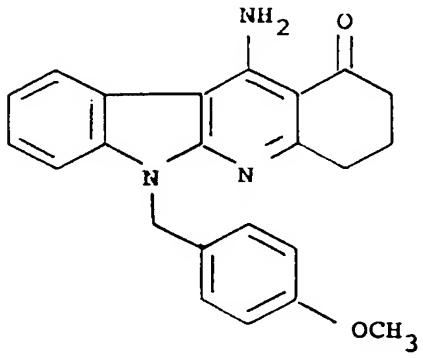


(D7)

The title compound (D7) was prepared from 5-phenyl-1,3-cyclohexanedione in 78% yield using a procedure similar to that described in Description 5 (Method B). Product was obtained as an off white solid. m.p. 168-170°.
NMR ($CDCl_3$) δ:
1.65-1.93 (4H, m), 2.40-2.57 (2H, m), 2.79-3.01 (4H, m), 3.15 -3.39 (2H, m), 3.39-3.57 (1H, m), 3.78 (3H, s), 5.28 (2H, s), 6.75-6.87 (2H, m), 7.00-7.14 (2H, m), 7.15-7.45 (5H, m).

Description 8

11-Amino-6-(4-methoxyphenyl)methyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one (D8)

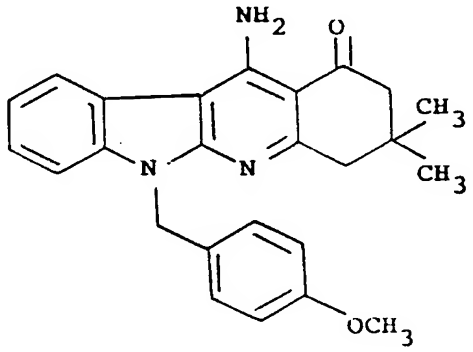


(D8)

The title compound (D8) was prepared from the intermediate D5 in 72% yield using a procedure similar to that described in EP-0249301A (Description 7) by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in toluene. Product was obtained as an off-white solid.
m.p. 194-7°.
NMR ($CDCl_3$) δ:
2.06-2.23 (2H, m), 2.64-2.79 (2H, m), 3.08-3.20 (2H, m), 3.76 (3H, s), 5.59 (2H, s), 6.80 (2H, d, J = 8Hz), 7.18 (2H, d, J = 8Hz), 7.23-7.40 (3H, m), 7.81 (1H, d, J = 8Hz).

Description 9

11-Amino-3,3-dimethyl-6-(4-methoxyphenyl)methyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one (D9)

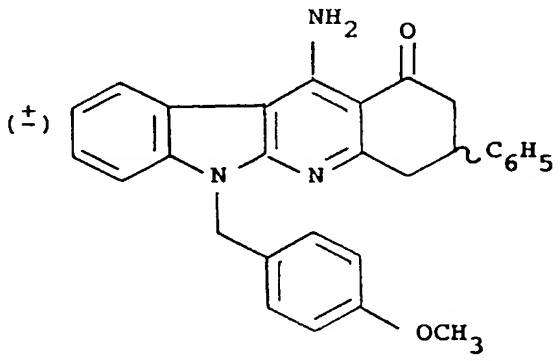


(D9)

The title compound (D9) was prepared from the intermediate D6 in 77% yield using a procedure similar to that described in Description 8. Product was obtained as an off-white solid.
NMR ($CDCl_3$) δ:
1.15 (6H, s), 2.58 (2H, s), 3.00 (2H, s), 3.75 (3H, s), 5.59 (2H, s) 6.74-6.82 (2H, m), 7.10-7.38 (5H, m), 7.74-7.83 (1H, m).

Description 10

(±) 11-Amino-6-(4-methoxyphenyl)methyl-3-phenyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one (D10)

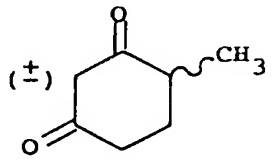


(D10)

The title compound (D10) was prepared from the intermediate D7 in 71% yield using a procedure similar to that described in Description 8. Product was obtained as a pale yellow solid. m.p. 163-5°.
NMR ($CDCl_3/D_6$ DMSO) δ:
2.85-3.00 (2H, m), 3.25-3.44 (2H, m), 3.44-3.63 (1H, m), 3.70 (3H, s), 5.57 (2H, s), 6.70-6.85 (2H, m), 7.11-7.45 (10H, m), 8.10-8.22 (1H, m).

Description 11

(±) 4-Methyl-1,3-cyclohexanedione (D11)



(D11)

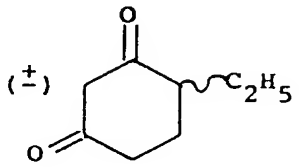
To a stirred solution of lithium diisopropylamide mono (tetrahydrofuran) (100ml, 150mM, 1.5M solution) in dry tetrahydrofuran (100ml) under an atmosphere of nitrogen and at -78°C was added dropwise 3-ethoxy-2-cyclohexen-1-one (21.0g, 150mM) dissolved in tetrahydrofuran (70ml) over a period of 15 min. After an additional 45 min, methyl iodide (21.29g, 150mM) dissolved in dry tetrahydrofuran (10ml) was added dropwise over a period of 5 min. After a further 15 min the cooling bath was removed and the whole stirred at room temperature for 1h. Water was then added and the enol ether intermediate recovered into ether, washed (brine), dried (Na_2SO_4) and evaporated to dryness. The oil thus obtained was dissolved in ethanol (100ml) and 5N hydrochloric acid (228ml) added. The whole was stirred at room temperature for 45 min. Water (800ml) was added, the aqueous phase made basic to pH 8-9 (NaOH) and extracted with ethyl acetate. The aqueous phase was re-acidified (HCl) and the product extracted into ethyl acetate. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated to give the title compound (D11) (17.6g) (92%) as an oil. Product could be used directly in the preparation of intermediate D13 without further purification.

The product could also be purified by distillation (bp 108-110°/1.5mmHg lit 110°/1mmHg (G.L. Burge D.J. Collins and J.D. Reitz, Aust. J. Chem., 1982, 35, 1913)
NMR ($CDCl_3$) δ:

1.22 (3H, d, J = 7Hz), 1.45-1.73 (1H, m), 1.95-2.28 (1H, m), 2.34-2.83 (3H, m), 3.32-3.58 (m, keto form), 4.19 (broad s, OH, enol form, variable with concentration), 5.5 (s, enol form)

Description 12

(±) 4-Ethyl-1,3-cyclohexanedione (D12)

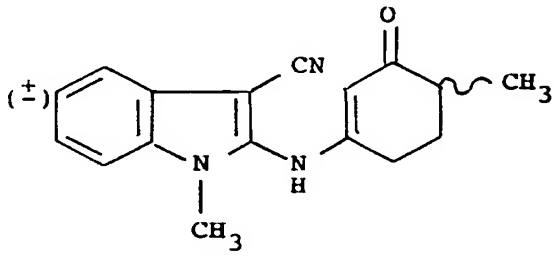


(D12)

The title compound (D12) was prepared from 3-ethoxy-2-cyclohexen-1-one and ethyl iodide using a procedure similar to that described in Description 11. Product was used in the preparation of D14 without further purification.

Description 13

(±) 2-[(4-methyl-3-oxo-1-cyclohexen-1-yl)amino]-1-methyl-1H-indole-3-carbonitrile (D13)

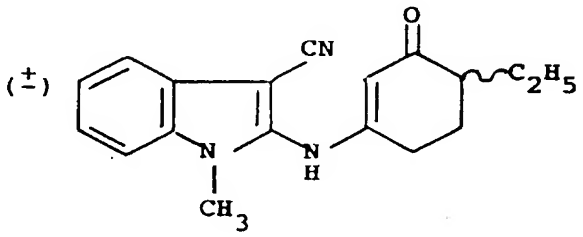


(D13)

The title compound (D13) was prepared from intermediates D3 and D11 in 61% yield using a procedure similar to that described in Description 1.
m.p. 194-5° (ethyl acetate).
NMR ($CDCl_3$) δ:
1.15 (3H, d, J = 11Hz), 1.68-1.95 (1H, m), 2.02-2.20 (1H, m), 2.23-2.43 (1H, m), 2.50-2.80 (2H, m), 3.59 (3H, s), 4.99 (1H, s), 7.10-7.50 (4H, m), 7.58-7.69 (1H, m)

Description 14

(±) 2-[(4-Ethyl-3-oxo-1-cyclohexen-1-yl)amino]-1-methyl-1H-indole-3-carbonitrile (D14)

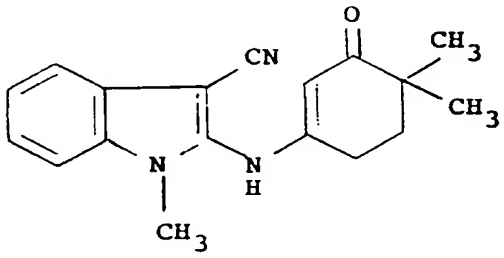


(D14)

The title compound (D14) was prepared from the intermediates D3 and D12 in 61% yield using a procedure similar to that described in Description 1. Product was purified by flash chromatography on t.l.c. silica with dichloromethane/ethyl acetate elution.
m.p. 205-6° (methanol)
NMR ($CDCl_3$) δ:
0.94 (3H, t, J = 8.5Hz), 1.30-1.58 (1H, m), 1.71-1.99 (2H, m), 2.05-2.28 (2H, m), 2.57-2.77 (2H, m), 3.60 (3H, s), 5.02 (1H, s), 7.17-7.49 (4H, m), 7.55-7.71 (1H, m)

Description 15

2-[(4,4-Dimethyl-3-oxo-1-cyclohexen-1-yl)amino]-1-methyl-1H-indole-3-carbonitrile (D15)

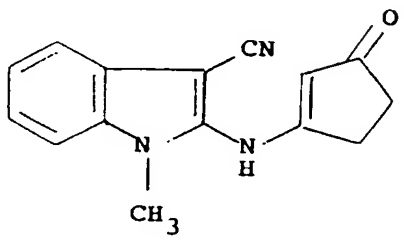


(D15)

The title compound (D15) was prepared from the intermediate D3 and 4,4-dimethyl-1,3-cyclohexanedione (K. Katsuura, K. Yamaguchi, S. Sakai and K. Mitsuhashi, Chem. Pharm. Bull, 1983, 31, 1518) in 86% yield using a procedure similar to that described in Description 1.
NMR ($CDCl_3$) δ:
0.83 (6H, s), 1.60 (2H, t, J = 6Hz), 2.39 (2H, t, J = 6Hz), 3.31 (3H, s), 4.59 (1H, s), 6.88-7.12 (3H, m), 7.28-7.38 (1H, m), 8.76 (1H, broad s).

Description 16

1-Methyl-2-[(3-oxo-1-cyclopenten-1-yl)amino]-1H-indole-3-carbonitrile (D16)

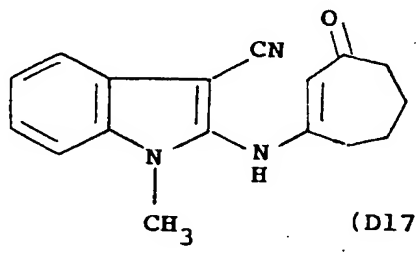


(D16)

The title compound (D16) was prepared from intermediate D3 and 1,3-cyclopropanedione in 61% yield using a procedure similar to that described in Description 1. Product was obtained as a solid.
NMR (D_6 DMSO) δ:
2.23-2.47 (2H, m), 2.74-2.93 (2H, m), 3.71 (3H, s), 5.09 (1H, m), 7.20-7.45 (2H, m), 7.51-7.72 (2H, m), 10.22 (1H, broad s).

Description 17

1-Methyl-2-[(3-oxo-1-cyclohepten-1-yl)amino]-1H-indole-3-carbonitrile (D17)

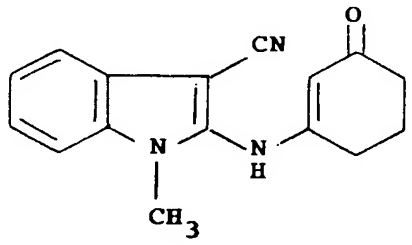


(D17)

The title compound (D17) was obtained during the preparation of compound E16 as described in Example 16.
NMR (D_6 DMSO) δ:
1.76-2.10 (4H, m), 2.48-2.65 (2H, m), 2.70-2.94 (2H, m), 3.62 (3H, s), 4.91 (1H, s), 7.12-7.50 (3H, m), 7.53-7.68 (1H, m), 8.80-9.09 (1H, broad s).

Description 18

1-Methyl-2-[(3-oxo-1-cyclohexen-1-yl)amino]-1H-indole-3-carbonitrile (D18)

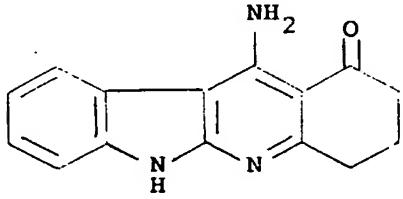


(D18)

The title compound (D18) was prepared from intermediate D3 and 1,3-cyclohexanedione in 60% yield using a procedure similar to that described in Description 1. The product was recrystallised from ethyl acetate.
M.p. 239-41°.
NMR ($CDCl_3$) δ:
2.02-2.19 (2H, m), 2.30-2.46 (2H, m), 2.55-2.70 (2H, m), 3.63 (3H, s), 5.04 (1H, s), 6.64 (1H, broad s), 7.22-7.42 (3H, m), 7.60-7.75 (1H, m).

Example 1

11-Amino-1,2,3,4-tetrahydro-6H-quinindolin-1-one (E1)



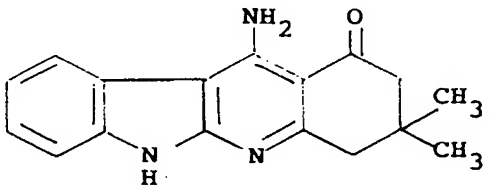
(E1)

The title compound (E1) was prepared from the intermediate D8 in 91% yield using a procedure similar to that described in EP 0249301A (Example 1, alternative procedure) by treatment with anisole, trifluoroacetic acid and concentrated sulphuric acid at room temperature. Product was obtained as a white solid.
m.p. >300°
NMR (D_6DMSO) δ:
2.05-2.20 (2H, m), 2.67-2.78 (2H, m), 3.04-3.17 (2H, m), 7.28-7.60 (3H, m plus 1H broad s), 8.40 (1H, d, J=8HZ), 9.50-9.89 (1H, broad s), 11.93 (1H, s).

Found:	C, 71.50;	H, 5.45;	N, 16.39%
$C_{15}H_{13}N_3O$ requires:	C, 71.70;	H, 5.21;	N, 16.72%

Example 2

11-Amino-3,3-dimethyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one (E2)

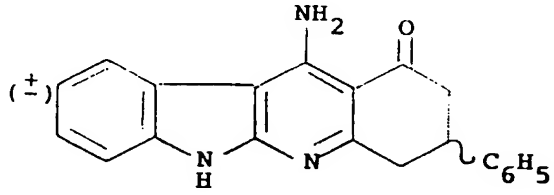


(E2)

The title compound (E2) was prepared from the intermediate D9 using a procedure similar to that described in EP 0249301A (Example 1, alternative procedure) by treatment with anisole, trifluoroacetic acid and concentrated sulphuric acid at room temperature. Product was obtained as a solid.
NMR (D_6 DMSO) δ:
1.20 (6H, s), 2.60 (2H, s), 3.06 (2H, s), 7.25-7.90 (3H, m plus 1H, broad s), 8.38-8.53 (1H, m), 9.50-10.05 (1H, broad s), 12.30 (1H, s).

Example 3

(±) 11-Amino-3-phenyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one (E3)



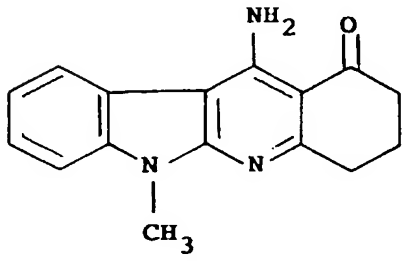
(E3)

The title compound (E3) was prepared from the intermediate D10 in 95% using a procedure similar to that described in Example 1. An analytical sample was obtained by boiling the solid in methanol, collecting the solid and drying in vacuo. m.p. >300°.
NMR (D_6 DMSO) δ:
2.77-2.93 (1H, m), 2.99-3.72 (4H, m), 7.20-7.70 (9H, m), 8.38-8.51 (1H, m), 9.46-9.88 (1H, broad s), 12.03 (1H, s).

Found:	C, 76.68;	H, 5.25;	N, 12.86%
$C_{21}H_{17}N_3O$ requires:	C, 77.04;	H, 5.23;	N, 12.84%.

Example 4

11-Amino-6-methyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one (E4)



(E4)

A suspension of compound E1 (8.48g, 32mM) in dry dimethylformamide (95ml) was added dropwise to a stirred suspension of 80% sodium hydride (35.2mM) in dimethylformamide (35ml) at 0° under N_2. After ¼h, methyl iodide (5.33g, 37.5mM) was added dropwise, and the solution allowed to stir at room temperature for approximately 16h. The solution was then poured onto water and extracted twice with dichloromethane. The combined organic phase was washed well with water, dried (Na_2SO_4) and evaporated to give a solid (9.71g). Recrystallization from methanol afforded the title compound (E4) (6.08g; 68%) as an off white solid. m.p. 145-6°.

NMR ($CDCl_3$)

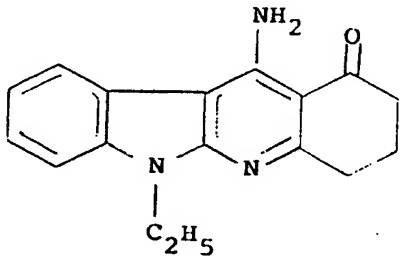
2.06-2.23 (2H, m), 2.63-2.80 (2H, m), 3.05-3.19 (2H, m), 3.90 (3H, s), 7.20-7.51 (3H, m), 7.80 (1H, d, J = 8Hz).

Found:	C, 72.32;	H, 5.82;	N, 15.74%
$C_{16}H_{15}N_3O$ requires:	C, 72.43;	H, 5.70;	N, 15.84%

Alternatively, example E4 can be prepared using intermediate D18 using a procedure similar to that described in Description 5.

Example 5

11-Amino-6-ethyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one (E5)



(E5)

The title compound (E5) was prepared from compound E1 and ethyl iodide in 66% using a procedure similar to that described in Example 4. Product was obtained as a white solid. m.p. 178-9°.

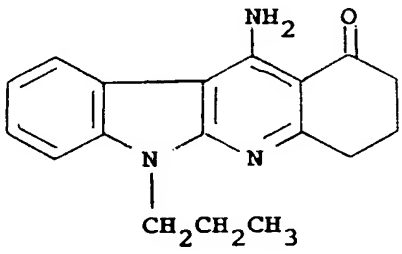
NMR ($CDCl_3$) δ:

1.42 (3H, t, J = 7.5Hz), 2.02-2.26 (2H, m), 2.58-2.80 (2H, m), 3.00-3.23 (2H, m), 4.49 (2H, q, J = 7.5Hz), 7.20-7.53 (3H, m), 7.70-7.90 (1H, m).

Found:	C, 73.51;	H, 6.44;	N, 15.07%
$C_{17}H_{17}N_3O$ requires:	C, 73.10;	H, 6.13;	N, 15.04%

Example 6

11-Amino-6-n-propyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one (E6)



(E6)

The title compound (E6) was prepared from compound E1 and 1-iodopropane in 39% yield using a procedure similar to that described in Example 4. Product was obtained as a white solid. m.p. 148-9°.

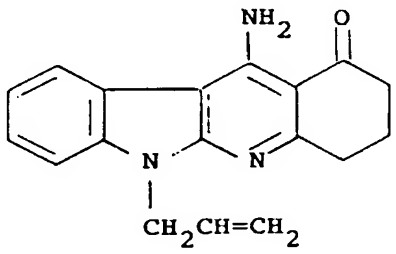
NMR ($CDCl_3$) δ:

0.98 (3H, t, J = 7.5Hz), 1.74-2.02 (2H, m), 2.05-2.27 (2H, m), 2.56-2.80 (2H, m), 3.01-3.22 (2H, m), 4.36 (2H, t, J = 7.5Hz), 7.18-7.55 (3H, m), 7.73-7.90 (1H, m).

Found:	C, 73.81;	H, 6.61;	N, 14.29%
$C_{18}H_{19}N_3O$ requires:	C, 73.69;	H, 6.53;	N, 14.32%

Example 7

11-Amino-6-(2-propenyl)-1,2,3,4-tetrahydro-6H-quinindolin-1-one (E7)



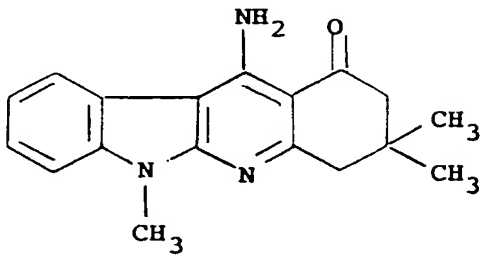
(E7)

The title compound (E7) was prepared from compound E1 and 3-bromopropene in 42% yield using a procedure similar to that described in Example 4. Product was obtained as a white solid. m.p. 132-3°.
NMR ($CDCl_3$ δ:
2.04-2.27 (2H, m), 2.56-2.80 (2H, m), 2.96-3.23 (2H, m), 4.90-5.30 (4H, m), 5.89-6.15 (1H, m), 7.20-7.50 (3H, m), 7.70-7.90 (1H, m).

Found:	C, 74.01;	H, 5.72;	N, 14.28%
$C_{18}H_{17}N_3O$ requires:	C, 74.20;	H, 5.88;	N, 14.42%

Example 8

11-Amino-1,2,3,4-tetrahydro-3,3,6-trimethyl-6H-quinindolin-1-one (E8)



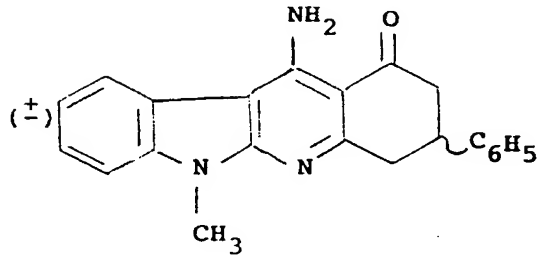
(E8)

The title compound (E8) was prepared from compound E2 in 44% using a procedure similar to that described in Example 4. Product was obtained as a white solid. m.p. 198-200°.
NMR ($CDCl_3$) δ:
1.13 (6H, s), 2.57 (2H, s), 3.00 (2H, s), 3.90 (3H, s), 7.21-7.50 (3H, m), 7.76-7.87 (1H, m).

Found:	C, 73.80;	H, 6.87;	N, 14.07%
$C_{18}H_{19}N_3O$ requires:	C, 73.69;	H, 6.53;	N, 14.32%

Example 9

(±) 11-Amino-6-methyl-3-phenyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one (E9)



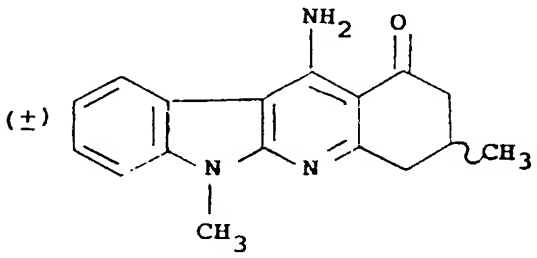
(E9)

The title compound (E9) was prepared from compound E3 in 50% yield using a procedure similar to that described in Example 4. Product was obtained as a white solid. m.p. 205-6°.
NMR ($CDCl_3$) δ:
2.87-3.08 (2H, m), 3.26-3.65 (3H, m), 3.92 (3H, s), 7.21-7.55 (8H, m), 7.80-7.90 (1H, m).

Found:	C, 77.21;	H, 5.53;	N, 12.32%
$C_{22}H_{19}N_3O$ requires:	C, 77.40;	H, 5.61;	N, 12.31%

Example 10

(±) 11-Amino-3,6-dimethyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one (E10)



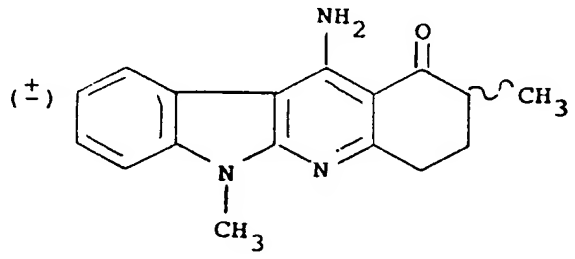
(E10)

The title compound (E10) was prepared from the intermediate D4 in 34.5% yield using a procedure similar to that described in Description 5 (Method A). Product was obtained as a white solid. m.p. 216-7°.
NMR ($CDCl_3$) δ:
1.09-1.24 (3H, m), 2.21-2.47 (2H, m), 2.50-3.30 (3H, m), 3.89 (3H, s), 7.20-7.32 (1H, m), 7.32-7.50 (2H, m), 8.09-8.21 (1H, m).

Found:	C, 73.35;	H, 6.28;	N, 15.05%
$C_{17}H_{17}N_3O$ requires:	C, 73.10;	H, 6.13;	N, 15.04%

Example 11

(±) 11-Amino-2,6-dimethyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one (E11)



(E11)

Method A

The title compound (E11) was prepared from the intermediate D13 in 41% yield using a procedure similar to that described in Description 6. Product was obtained as an off white solid m.p. 155-6.5°. The product could also be purified via preparation of the tartrate salt followed by liberation of the free base.

NMR ($CDCl_3$) δ:

1.31 (3H, d, J = 11Hz), 1.80-2.03 (1H, m), 2.11-2.30 (1H, m), 2.55-2.78 (1H, m), 3.04-3.31 (2H, m), 3.90 (3H, s), 7.21-7.53 (3H, m), 7.73-7.89 (1H, m)

found:	C, 73.16;	H, 6.14;	N, 15.02%
$C_{17}H_{17}N_3O$ requires:	C, 73.10;	H, 6.13;	N, 15.04%.

The racemic mixture obtained was separated into the two enantiomers by the use of analytical H.P.L.C. using the following conditions:

Column: Chiral-A.G.P. 4.0x100mm; ID = 18RC
Eluent: 20/80 CH_3OH/0.02M aqueous phosphate buffer at pH 7.0.
Flow: 1.0ml/min.
Detection: U.V. at 278 nm.

The retention times of the enantiomers under these conditions were 34.0 and 42.2 minutes respectively.

Method B

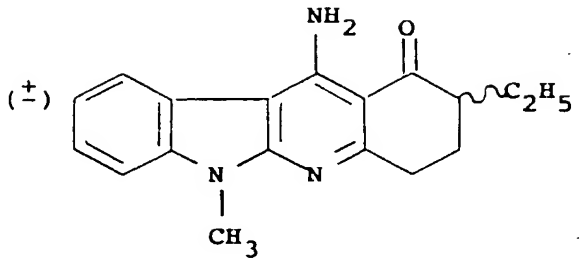
To a solution of the compound E4 (0.50g, 1.88mM) in dry tetrahydrofuran (17ml) at -78° and under an atmosphere of nitrogen, was added lithium diisopropylamide mono (tetrahydrofuran) (3ml, 3.8mM, 1.5M solution) over a period of 10 minutes. The whole was stirred at -78° for an additional 45 minutes before methyl iodide (0.12ml, 1.88mM) was added. The whole was held at this temperature for an additional 1h before the cooling bath was removed. After an additional 30 minutes water (30ml) was added and product was extracted into dichloromethane (3 x 50ml). The organic phase was washed with brine (50ml), dried (Na_2SO_4) and evaporated to dryness to give the title compound (E11) (0.47g 89%) which was in the preparation of E15 without further purification.

NMR ($CDCl_3$) δ:

1.31 (3H, d, J = 11Hz), 1.80-2.01 (1H,m), 2.11-2.30 (1H, m), 2.54-2.77 (1H, m), 3.05-3.30 (2H, m), 3.89 (3H, s), 7.20-7.52 (3H, m), 7.72-7.88 (1H, m).

Example 12

(±) 11-Amino-2-ethyl-6-methyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one (E12)



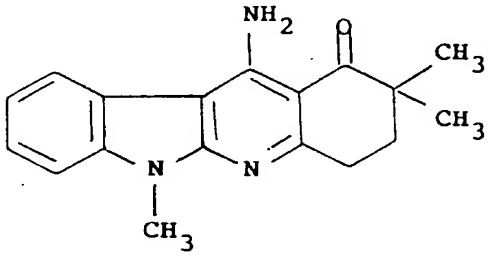
(E12)

The title compound (E12) was prepared from the intermediate D14 in 66% yield using a procedure similar to that described in Description 6. Product was obtained as a buff coloured solid.
m.p. 129-131° (ethyl acetate-petroleum ether (60-80)).
NMR ($CDCl_3$) δ:
1.06 (3H, t, J = 7Hz), 1.50-1.75 (1H, m), 1.80-2.13 (2H, m), 2.16-2.35 (1H, m), 2.38-2.57 (1H, m), 2.98-3.33 (2H, m), 3.89 (3H, s), 7.21-7.50 (3H, m), 7.71-7.88 (1H, m)

Found:	C, 73.87;	H, 6.72;	N, 14.09%
$C_{18}H_{19}N_3O$ requires:	C, 73.69;	H, 6.53;	N, 14.32%

Example 13

11-Amino-1,2,3,4-tetrahydro-2,2,6-trimethyl-6H-quinindolin-1-one (E13)



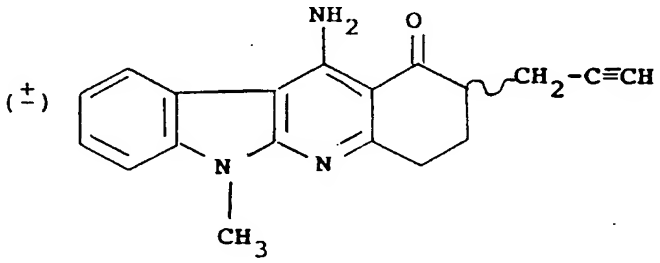
(E13)

The title compound (E13) was prepared from the intermediate D15 in 53% yield using a procedure similar to that described in Description 6. Crystallisation from methanol gave the title compound (E13) 53% as a buff coloured solid.
m.p. 188-9°
NMR ($CDCl_3$) δ:
1.29 (6H, s), 2.00 (2H, t, J = 6Hz), 3.19 (2H, J = 6Hz), 3.89 (3H, s), 7.21-7.35 (1H, m), 7.36-7.52 (2H, m), 7.72-7.87 (1H, m).

Found:	C, 73.61;	H, 6.59;	N, 14.36%
$C_{18}H_{19}N_3O$ requires:	C, 76.69;	H, 6.53;	N, 14.32%

Example 14

(±) 11-Amino-6-methyl-2-(2-propynyl)-1,2,3,4-tetrahydro-6H-quinindolin-1-one (E14)



(E14)

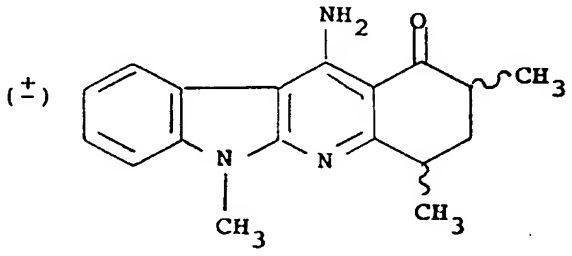
The title compound (E14) was prepared from the compound E4 and propargyl bromide in 55% yield using a procedure similar to that described in Example 11 (Method B). Product was obtained as an off white solid (CH_3OH).

NMR ($CDCl_3$) δ:

2.00-2.30 (2H, m), 2.46-2.73 (2H, m), 2.73-2.90 (1H, m), 2.92-3.11 (1H, m), 3.11-3.42 (2H, m), 3.97 (3H, s), 7.32-7.60 (3H, m), 7.80-7.95 (1H, m)

Example 15

(±) 11-Amino-1,2,3,4-tetrahydro-2,4,6-trimethyl-6H-quinindolin-1-one (E15)



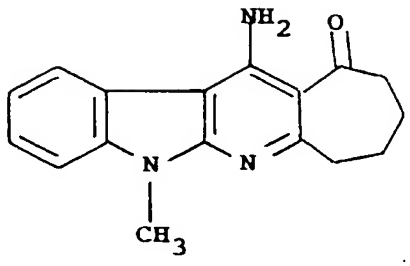
(E15)

To a solution of compound E11, (method B) (0.47g, 1.68mM) in dry tetrahydrofuran (20ml) under an atmosphere of nitrogen and at -78° was added dropwise lithium diisopropylamide mono(tetrahydrofuran) (2.6ml, 3.7mM, 1.5M solution) over a period of 5 minutes. The whole was then stirred at -78° for a further 30 minutes followed by -40° for 30 minutes. After re-cooling to -78°, methyl iodide (0.1ml, 1.68mM) in dry THF (5ml) was added dropwise over 2 minutes. The whole was stirred at this temperature for an additional 10 minutes, before the cooling bath was removed and the whole allowed to warm to room temperature. Water (50ml) was then added and the product extracted into dichloromethane (3 x 50ml). The organic phase was washed with brine (50ml), dried (Na_2SO_4) and evaporated to dryness to give a crude product (0.50g). Product was purified by flash chromatography on t.l.c. silica with petroleum ether (60-80)/ethyl acetate

elution to give the title compound (E15) (0.22g, 44%) Rf 0.47 (SiO_2, 30% ethyl acetate, 70% petroleum ether (60-80)) which was converted to the tartrate salt (0.18g).
m.p. 206-11° (ethanol).
NMR (D_6DMSO) δ:
1.19 (3H, d, J=7Hz), 1.41 (3H, d, J=7Hz), 1.81-2.09 (2H, m), 2.69-2.91 (1H, m), 3.05-3.28 (1H, m), 3.81 (3H, s), 4.31 (tartrate), 7.05-7.47 (2H, m, plus 1H broad singlet), 7.48-7.62 (1H, m), 8.23-8.39 (1H, m), 9.68 (1H, broad s).
MS measured 293.1537, calculated for $C_{18}H_{19}N_3O$293.1528.

Example 16

12-Amino-7-methyl-cyclohepta[5,6]pyrido[2,3-b]indol-1-one (E16)



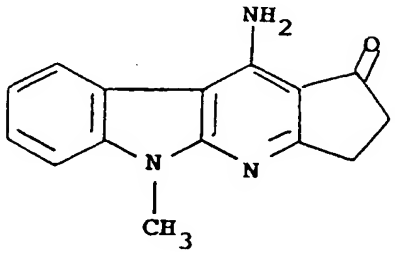
(E16)

To a solution of the intermediate D3 (32.2mM) and para-toluenesulphonic acid (0.53g, 2.78mM) in toluene (200ml), heated under vigorous reflux with water removal, was added dropwise over a period of ½h, 1,3-cycloheptadione (3.01g, 23.9mM) (CA, 101, 151464j) dissolved in toluene (50ml). After an additional ¾h the solution was allowed to cool and poured onto saturated aqueous sodium bicarbonate solution. The toluene layer was separated and the aqueous layer extracted with ethyl acetate containing ca. 5% methanol (x3). The combined organic phase was washed with saturated brine, dried (Na_2SO_4) and evaporated to dryness to afford a brown oil containing a mixture of compounds. Chromatography (SiO_2, dichloromethane/ethyl acetate) afforded the title compound (E16) (1.78g, 27%) Rf 0.57 (SiO_2 2:1 dichloromethane:ethyl acetate) as a pale yellow solid m.p. 124-6°C (ethyl acetate-petroleum ether 60-80).

Also isolated by chromatography was [(3-oxo-1-cyclohepten-1-yl)amino]-1-methyl-1H-indole-3-carbonitrile (D17) (1.30g, 20%) Rf 0.19 (SiO_2, 2:1 dichloromethane:ethyl acetate). This intermediate could be converted to the title compound (E16) using a procedure similar to that described in Description 6.
NMR ($CDCl_3$) δ:
1.77-2.10 (4H, m), 2.78-2.94 (2H, m), 3.12-3.30 (2H, m), 3.92 (3H, s), 6.90-7.60 (5H, m), 7.77-7.90 (1H, m).

Example 17

10-Amino-5-methyl-cyclopenta[5.6]pyrido[2,3-b]indol-1-one (E17)



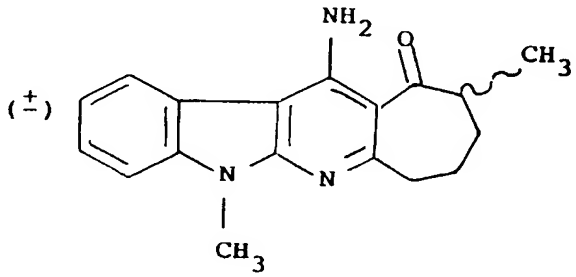
(E17)

The title compound (E17) was prepared from the intermediate D16 in 60% yield using a procedure similar to that described in Description 6. Product was obtained as a pale green solid. m.p. 279-80°.
NMR ($CDCl_3$) δ:
2.67-2.84 (2H, m), 3.07-3.25 (2H, m), 3.91 (3H, s), 6.10-7.15 (2H, broad s), 7.20-7.56 (3H, m), 7.72-7.88 (1H, m).

Found:	C, 71.72;	H, 5.47;	N, 16.68%
$C_{15}H_{13}N_3O$ requires:	C, 71.70;	H, 5.21;	N, 16.72%

Example 18

(±) 12-Amino-2,7-dimethyl-cyclohepta[5,6]pyrido[2,3-b]indol-1-one (E18)



(E18)

The title compound (E18) was prepared from compound E16 using a procedure similar to that described in Example 11 (Method B).
MS measured 293.1526, calculated for $C_{18}H_{19}N_3O$293.1528.

Pharmacological Data

Geller-Seifter Procedure

Potential anxiolytic properties have been evaluated using the Geller-Seifter procedure based on that originally described by Geller and Seifter (1960) Psychopharmacologia, 1, 482-492. This procedure has

been shown to be selective for drugs with anxiolytic properties (Cook and Sepinwall (1975) 'Mechanism of Action of Benzodiazepines' ed. Costa, E. and Greengard, P., Raven Press, New York, pp. 1-28).

Rats are trained on a variable interval 30 sec schedule (VI30) to press a lever in order to obtain food reward. The 3 min sessions of the VI30 schedule alternate with 3 min of a schedule (FR5) in which every 5th lever press is followed by a presentation of a food pellet paired with a 0.2 sec mild footshock. The amplitude of the shock is adjusted for each rat to give equivalent response rates. The total study consists of VI and FR components and lasts 30 mins. Rats typically respond with high rates of lever pressing under the VI30 schedule and low response rats under the FR5 'conflict' session. Anxiolytic drugs increase the suppressed response rates of rats in 'conflict' sessions.

The compound is administered intraperitoneally or orally to groups of 6-16 rats 30 min (intraperitoneal route) or 60 min (oral route) before testing.

The results are expressed as the percentage increase in square root of the total number of lever presses in the FR5 'conflict' sessions. Square root transformation is necessary to normalise the data for statistical analysis using parametric methods. A change in the square root of the VI can indicate non-specific drug effects i.e. stimulation or sedation.

Testing Results

The following compounds have shown activity in the above tests as detailed in the Table 1.

Table 1

Compound	Dose mg/kg	increase in responding in the 'conflict' session
E1	20 p.o.	+16%
E4	20 p.o.	+29%
E5	20 p.o.	+29%
E6	20 p.o.	+17%
E7	20 p.o.	+16%
E10	20 p.o.	+17%
E11	20 p.o.	+52%
E12	20 p.o.	+33%
E13	20 p.o.	+21%
E16	20 p.o.	+11%
E17	100 p.o.	+37%

[^{35}S]-TBPS binding to rat cerebral cortex membranes in vitro

[^{35}S]-TBPS labels a site on or near the Cl^- channel portion of the $GABA_A$/BDZ/Cl^- channel complex. Literature studies have shown that [^{35}S]-TBPS binding is directly related to the permeability of the Cl^- channel (e.g. Concas et al, 1988). Anxiolytic agents such as benzodiazepines and barbiturates allosterically inhibit the binding, whilst anxiogenic agents (e.g. benzodiazepine inverse agonists) potentiate the binding.

Modulation of [^{35}S]-TBPS binding is measured by a method similar to that of Gee et al (1986).

Pooled rat cerebral cortices were homogenised in 20 volumes of 0.32M sucrose and centrifuged at 1000g for 20 minutes (4°C). The supernatant was removed and recentrifuged at 50,000g (4°C, 20 mins). The P_2 pellet was then suspended in 20 volumes of Tris citrate buffer (pH 7.1) and centrifuged at 50,000g (4°C, 20 mins). This washing step was repeated three times and the pellet finally resuspended in 20 volumes of buffer and stored at -70°C prior to use.

The tissue suspension (50µl) was incubated (25°C, 120 mins) with [^{35}S]-TBPS (2nM) in Tris citrate buffer (pH 7.1) containing 0.2M NaCl and 5 x 10^{-6}M GABA. Non-specific binding was measured in the presence of 10^{-4}M picrotoxin. Varying concentrations of test drugs (10^{-7}, 10^{-6}, 10^{-5} and 10^{-4}M final concentration) were added in a volume of 50µl. The total assay volume was 500µl. Incubation was stopped by rapid filtration using a Skatron cell harvester and radioactivity measured by liquid scintillation spectrometry. IC_{50}'s were calculated as the concentration of test drug to inhibit 50% of specific binding.

Concas A. et al, (1988) J. Neurochem. 51(6), 1868-1876. Gee K.W. et al, (1986) Mol. Pharmacol. 30, 218-225.

The results are shown in Table 2.

Table 2

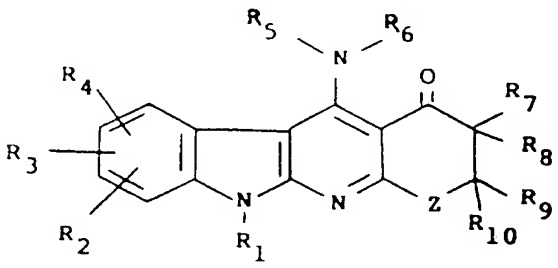
Compound	[^{35}S]-TBPS IC_{50} μM
E5	7.5^{+}
E6	3.8^{+}
E7	1.9*
E8	4.4^{+}
E11	1.2* (n = 2)
E12	1.4*
E13	1.7* (n = 2)
E14	1.0*
E15	3.8* (n = 2)
E16	3.3*

* done in the presence of GABA
$^{+}$ done in the absence of GABA

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, GR, IT, LI, LU, NL, SE

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R_1 is hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-4} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl;

R_2, R_3 and R_4 are independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, C_{1-6} alkylthio, hydroxy, C_{2-7} alkanoyl, chloro, fluoro, trifluoromethyl, nitro, amino optionally substituted by one or two C_{1-6} alkyl groups or by C_{2-7} alkanoyl, cyano, carbamoyl and carboxy, and phenyl, phenyl C_{1-4} alkyl or phenyl C_{1-4} alkoxy in which any phenyl moiety is optionally substituted by any of these groups;

R_5 and R_6 are independently selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-4} alkyl, C_{2-6} alkenyl, C_{1-7} alkanoyl, C_{1-6} alkylsulphonyl, di-(C_{1-6} alkyl)amino C_{1-6} alkyl, 3-oxobutyl, 3-hydroxybutyl, and phenyl, phenyl C_{1-4} alkyl, benzoyl, phenyl C_{2-7} alkanoyl or benzenesulphonyl any of which phenyl moieties are optionally substituted by one or two halogen, C_{1-6} alkyl, C_{1-6} alkoxy, CF_3, amino or carboxy, or R_5 and R_6 together are C_{2-6} polymethylene optionally interrupted by oxygen or NR_{11} wherein R_{11} is hydrogen or C_{1-6} alkyl optionally substituted by hydroxy;

R_7, R_8, R_9 and R_{10} are independently selected from hydrogen, C_{1-8} alkyl optionally substituted by one or two hydroxy, oxo, C_{1-4} alkoxy, halogen or CF_3 groups, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-4} alkyl, C_{2-7} alkanoyl, C_{2-6} alkenyl or C_{2-6} alkynyl either being optionally substituted by one, two or three halogen atoms or C_{1-4} alkyl, C_{3-7} cycloalkenyl optionally substituted by one or two halogen or C_{1-4} alkyl groups, C_{3-7} cycloalkenyl-C_{1-4} alkyl in which the cycloalkenyl ring is optionally substituted by one or two halogen or C_{1-4} alkyl groups, and phenyl optionally substituted by one or two halogen, C_{1-6} alkyl, C_{1-6} alkoxy, CF_3, amino or carboxy,

or R_7 and R_8 together and/or R_9 and R_{10} together are C_{3-6} polymethylene optionally substituted by C_{1-6} alkylor C_{2-6} alkenyl; and

Z is $(CR_{14}R_{15})_n$ where n is 0, 1 or 2 and R_{14} and R_{15} are independently selected from hydrogen, C_{1-6} alkyl or C_{2-6} alkenyl.

2. A compound according to claim 1, wherein R_2, R_3 and R_4 are hydrogen.

3. A compound according to claim 1 or 2, wherein R_5 is hydrogen and R_6 is hydrogen or C_{1-6} alkyl.

4. A compound according to any one of claims 1 to 3, wherein R_1 is hydrogen, methyl, ethyl, propyl or prop-2-enyl.

5. A compound according to any one of claims 1 to 4, wherein R_7 is hydrogen, methyl or ethyl and R_8 is hydrogen or methyl.

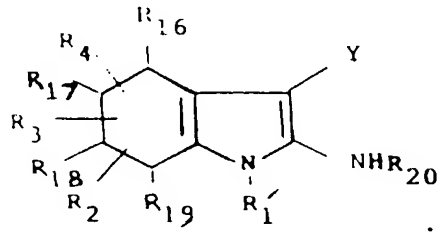
6. A compound according to any one of claims 1 to 5, wherein R_9 is hydrogen or methyl and R_{10} is hydrogen, methyl or phenyl.

7. A compound according to any one of claims 1 to 6 wherein n in Z is 1 or 2, R_{14} is hydrogen and R_{15} is hydrogen or methyl.

8. A compound according to any one of claims 1 to 7, wherein n in Z is 1.

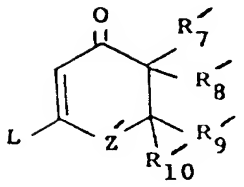
9. 11-Amino-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
11-amino-3,3-dimethyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
(±) 11-amino-3-phenyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
11-amino-6-methyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
11-amino-6-ethyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
11-amino-6-n-propyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
11-amino-6-(2-propenyl)-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
11-amino-1,2,3,4-tetrahydro-3,3,6-trimethyl-6H-quinindolin-1-one,
(±) 11-amino-6-methyl-3-phenyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
(±) 11-amino-3,6-dimethyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
(±) 11-amino-2,6-dimethyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
(+) 11-amino-2,6-dimethyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
(-) 11-amino-2,6-dimethyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
(±) 11-amino-2-ethyl-6-methyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
11-amino-1,2,3,4-tetrahydro-2,2,6-trimethyl-6H-quinindolin-1-one,
(±) 11-amino-6-methyl-2-(2-propynyl)-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
(±) 11-amino-1,2,3,4-tetrahydro-2,4,6-trimethyl-6H-quinindolin-1-one,
12-amino-7-methyl-cyclohepta[5,6]pyrido[2,3-b]indol-1-one,
10-amino-5-methyl-cyclopenta[5,6]pyrido[2,3-b]indol-1-one or
(±) 12-amino-2,7-dimethyl-cyclohepta[5,6]pyrido[2,3-b]indol-1-one or a pharmaceutically acceptable salt of any of the foregoing compounds.

10. A process for the preparation of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, which process comprises the condensation of a compound of formula (IV):



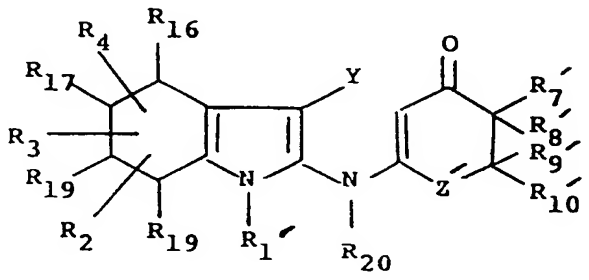
(IV)

with a compound of formula (V):



(V)

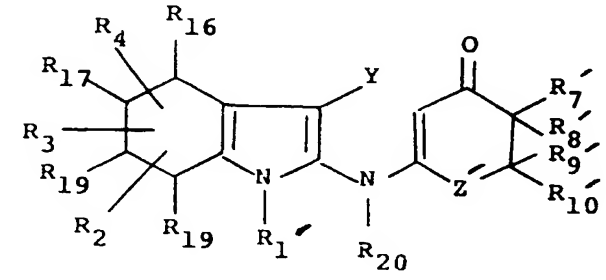
wherein R_1' is R_1 as defined in claim 1 or an N-protecting group, R_2, R_3 and R_4 are as defined in claim 1, R_{16}, R_{17}, R_{18} and R_{19} are each hydrogen or R_{16} and R_{17}, and R_{18} and R_{19} together represent a bond, L is a leaving group, Y is a group CN or COL_1, where L_1 is a leaving group, R_{20} is hydrogen or an N-protecting group and R_7', R_8', R_9', R_{10}' and Z' are R_7, R_8, R_9, R_{10} and Z respectively, as defined in claim 1 or a group convertible to R_7, R_8, R_9, R_{10} and Z, respectively, to give an acyclic enamine intermediate of formula (VI):



(VI)

wherein Y, R_1', R_2, R_3, R_4, R_{16}, R_{17}, R_{18}, R_{19} and R_{20} are as defined in formula (IV) and R_7', R_8', R_9', R_{10}' and Z' are as defined in formula (V); and thereafter, optionally or as necessary, and in any appropriate order, cyclising the enamine intermediate, separating any enantiomers, converting R_{20} when hydrogen to an N-protecting group, converting R_7', R_8', R_9', R_{10}' and Z' to R_7, R_8, R_9, R_{10} and Z, respectively, when Y is a group COL_1, converting the resulting hydroxy group to a leaving group and reacting the latter with a compound HNR_5R_6, removing any R_1' N-protecting group, removing any R_{20} N-protecting group, converting R_{16}, R_{17}, R_{18} and R_{19} when hydrogen to two bonds, interconverting R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10} or Z and/or forming a pharmaceutically acceptable salt of the compound of formula (I).

11. A compound of formula (VI) or a salt thereof:

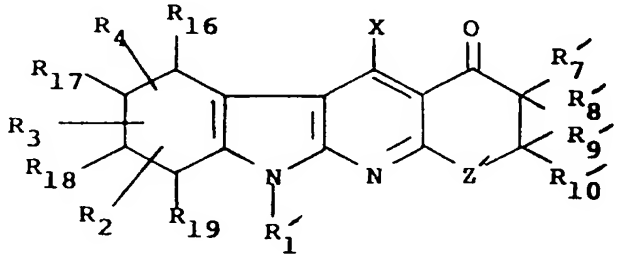


(VI)

wherein Y, R_1', R_2, R_3, R_4, R_7', R_8', R_9', R_{10}', R_{16}, R_{17}, R_{18}, R_{19}, R_{20} and Z are as defined in claim 10.

12. 1-(4-Methoxyphenyl)methyl-2-[(3-oxo-1-cyclohexen-1-yl)amino]-4,5,6,7-tetrahydro-1H-indole-3-carbonitrile,
2-[(5,5-dimethyl-3-oxo-1-cyclohexen-1-yl)amino]-1-(4-methoxyphenyl)methyl-4,5,6,7-tetrahydro-1H-indole-3-carbonitrile,
(±) 2-[(5-methyl-3-oxo-1-cyclohexen-1-yl)amino]-1-methyl-1H-indole-3-carbonitrile,
(±) 2-[(4-methyl-3-oxo-1-cyclohexen-1-yl)amino]-1-methyl-1H-indole-3-carbonitrile,
(±) 2-[(4-ethyl-3-oxo-1-cyclohexen-1-yl)amino]-1-methyl-1H-indole-3-carbonitrile,
2-[(4,4-dimethyl-3-oxo-1-cyclohexen-1-yl)amino]-1-methyl-1H-indole-3-carbonitrile,
1-methyl-2-[3-oxo-1-cyclopenten-1-yl)amino]-1H-indole-3-carbonitrile,
1-methyl-2-[(3-oxo-1-cycloheptен-1-yl)amino]-1H-indole-3-carbonitrile or
1-methyl-2-[(3-oxo-1-cyclohexen-1-yl)amino]-1H-indole-3-carbonitrile.

13. A compound of formula (VII) or a salt thereof:



(VII)

wherein X is NH_2, OH or chloro, R_1', R_2, R_3, R_4, R_7', R_8', R_9', R_{10}', R_{16}, R_{17}, R_{18}, R_{19} and Z' are as defined in claim 10, with the proviso that when R_1', R_7', R_8', R_9', R_{10}', and Z' are R_1, R_7, R_8, R_9, R_{10} and Z as defined in claim 1 and R_{16} and R_{17}, and R_{18} and R_{19} together represent a bond, X is not NH_2.

14. 11-Amino-6-(4-methoxyphenyl)methyl-1,2,3,4,7,8,9,10-octahydro-6H-quinindolin-1-one,
11-amino-3,3-dimethyl-6-(4-methoxyphenyl)methyl-1,2,3,4,7,8,9,10-octahydro-6H-quinindolin-1-one,
(±) 11-amino-6-(4-methoxyphenyl)methyl-1,2,3,4,7,8,9,10-octahydro-3-phenyl-6H-quinindolin-1-one,
11-amino-6-(4-methoxyphenyl)methyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
11-amino-3,3-dimethyl-6-(4-methoxyphenyl)methyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one or
(±) 11-amino-6-(4-methoxyphenyl)methyl-3-phenyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one.

15. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 9 and a pharmaceutically acceptable carrier.

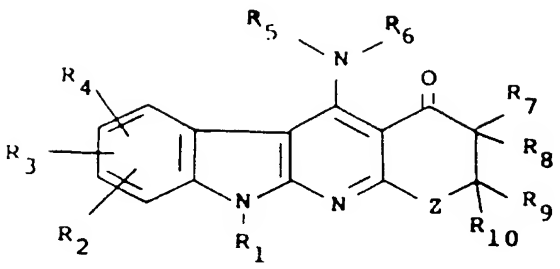
16. A compound according to any one of claims 1 to 9, for use as an active therapeutic substance.

17. A compound according to any one of claims 1 to 9, for use in the treatment of anxiety or depression in mammals.

18. Use of a compound according to any one of claims 1 to 9, in the manufacture of a medicament for the treatment of anxiety or depression in mammals.

Claims for the following Contracting State : ES

1. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R_1 is hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-4} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl;

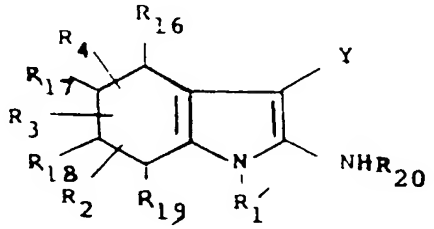
R_2, R_3 and R_4 are independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, C_{1-6} alkylthio, hydroxy, C_{2-7} alkanoyl, chloro, fluoro, trifluoromethyl, nitro, amino optionally substituted by one or two C_{1-6} alkyl groups or by C_{2-7} alkanoyl, cyano, carbamoyl and carboxy, and phenyl, phenyl C_{1-4} alkyl or phenyl C_{1-4} alkoxy in which any phenyl moiety is optionally substituted by any of these groups;

R_5 and R_6 are independently selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-4} alkyl, C_{2-6} alkenyl, C_{1-7} alkanoyl, C_{1-6} alkylsulphonyl, di-(C_{1-6} alkyl)amino C_{1-6} alkyl, 3-oxobutyl, 3-hydroxybutyl, and phenyl, phenyl C_{1-4} alkyl, benzoyl, phenyl C_{2-7} alkanoyl or benzenesulphonyl any of which phenyl moieties are optionally substituted by one or two halogen, C_{1-6} alkyl, C_{1-6} alkoxy, CF_3, amino or carboxy, or R_5 and R_6 together are C_{2-6} polymethylene optionally interrupted by oxygen or NR_{11} wherein R_{11} is hydrogen or C_{1-6} alkyl optionally substituted by hydroxy;

R_7, R_8, R_9 and R_{10} are independently selected from hydrogen, C_{1-8} alkyl optionally substituted by one or two hydroxy, oxo, C_{1-4} alkoxy, halogen or CF_3 groups, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-4} alkyl, C_{2-7} alkanoyl, C_{2-6} alkenyl or C_{2-6} alkynyl either being optionally substituted by one, two or three halogen atoms or C_{1-4} alkyl, C_{3-7} cycloalkenyl optionally substituted by one or two halogen or C_{1-4} alkyl groups, C_{3-7} cycloalkenyl-C_{1-4} alkyl in which the cycloalkenyl ring is optionally substituted by one or two halogen or C_{1-4} alkyl groups, and phenyl optionally substituted by one or two halogen, C_{1-6} alkyl, C_{1-6} alkoxy, CF_3, amino or carboxy,

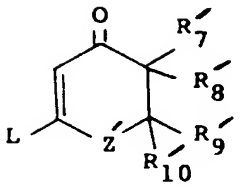
or R_7 and R_8 together and/or R_9 and R_{10} together are C_{3-6} polymethylene optionally substituted by C_{1-6} alkylor C_{2-6} alkenyl; and

Z is $(CR_{14}R_{15})_n$ where n is 0, 1 or 2 and R_{14} and R_{15} are independently selected from hydrogen, C_{1-6} alkyl or C_{2-6} alkenyl, which process comprises the condensation of a compound of formula (IV):



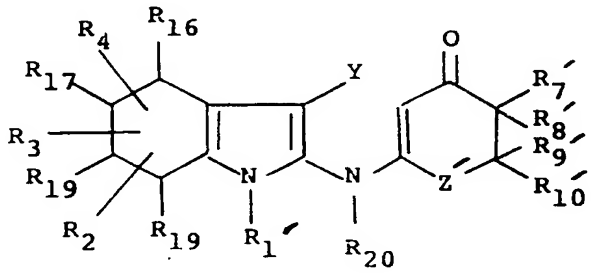
(IV)

with a compound of formula (V):



(V)

wherein R_1' is R_1 as defined in formula (I) or an N-protecting group, R_2, R_3 and R_4 are as defined in formula (I), R_{16}, R_{17}, R_{18} and R_{19} are each hydrogen or R_{16} and R_{17}, and R_{18} and R_{19} together represent a bond, L is a leaving group, Y is a group CN or COL_1, where L_1 is a leaving group, R_{20} is hydrogen or an N-protecting group and R_7', R_8', R_9', R_{10}' and Z' are R_7, R_8, R_9, R_{10} and Z respectively, as defined in formula (I) or a group convertible to R_7, R_8, R_9, R_{10} and Z, respectively, to give an acyclic enamine intermediate of formula (VI):



(VI)

wherein Y, R_1', R_2, R_3, R_4, R_{16}, R_{17}, R_{18}, R_{19} and R_{20} are as defined in formula (IV) and R_7', R_8', R_9', R_{10}' and Z' are as defined in formula (V); and thereafter, optionally or as necessary, and in any appropriate order, cyclising the enamine intermediate, separating any enantiomers, converting R_{20} when hydrogen to an N-protecting group, converting R_7', R_8', R_9', R_{10}' and Z' to R_7, R_8, R_9, R_{10} and Z, respectively, when Y is a group COL_1, converting the resulting hydroxy group to a leaving group and reacting the latter with a compound HNR_5R_6, removing any R_1' N-protecting group, removing any R_{20} N-protecting group, converting R_{16}, R_{17}, R_{18} and R_{19} when hydrogen to two bonds, interconverting R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10} or Z and/or forming a pharmaceutically acceptable salt of the compound of formula (I).

2. A process according to claim 1, for the preparation of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, wherein R_2, R_3 and R_4 are hydrogen.

3. A process according to claim 1 or 2, for the preparation of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, wherein R_5 is hydrogen and R_6 is hydrogen or C_{1-6} alkyl.

4. A process according to any one of claims 1 to 3, for the preparation of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, wherein R_1 is hydrogen, methyl, ethyl, propyl or prop-2-enyl.

5. A process according to any one of claims 1 to 4, for the preparation of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, wherein R_7 is hydrogen, methyl or ethyl and R_8 is hydrogen or methyl.

6. A process according to any one of claims 1 to 5, for the preparation of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, wherein R_9 is hydrogen or methyl and R_{10} is hydrogen, methyl or phenyl.

7. A process according to any one of claims 1 to 6, for the preparation of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, wherein n in Z is 1 or 2, R_{14} is hydrogen and R_{15} is hydrogen or methyl.

8. A process according to any one of claims 1 to 7, for the preparation of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, wherein n in Z is 1.

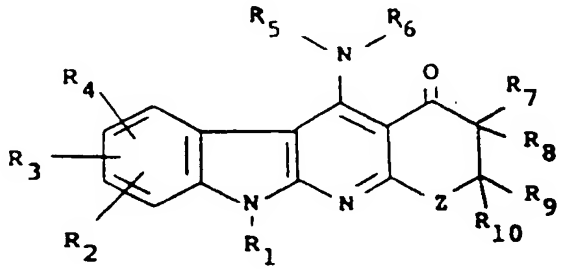
9. A process according to any one of claims 1 to 7, for the preparation of a compound of formula (I) which is:
1-amino-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
11-amino-3,3-dimethyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
(±) 11-amino-3-phenyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
11-amino-6-methyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
11-amino-6-ethyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
11-amino-6-n-propyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
11-amino-6-(2-propenyl)-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
11-amino-1,2,3,4-tetrahydro-3,3,6-trimethyl-6H-quinindolin-1-one,
(±) 11-amino-6-methyl-3-phenyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
(±) 11-amino-3,6-dimethyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
(±) 11-amino-2,6-dimethyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
(+) 11-amino-2,6-dimethyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
(-) 11-amino-2,6-dimethyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
(±) 11-amino-2-ethyl-6-methyl-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
11-amino-1,2,3,4-tetrahydro-2,2,6-trimethyl-6H-quinindolin-1-one,
(±) 11-amino-6-methyl-2-(2-propynyl)-1,2,3,4-tetrahydro-6H-quinindolin-1-one,
(±) 11-amino-1,2,3,4-tetrahydro-2,4,6-trimethyl-6H-quinindolin-1-one,
12-amino-7-methyl-cyclohepta[5,6]pyrido[2,3-b]indol-1-one;
10-amino-5-methyl-cyclopenta[5,6]pyrido[2,3-b]indol-1-one or
(±) 12-amino-2,7-dimethyl-cyclohepta[5,6]pyrido[2,3-b]indol-1-one, or a pharmaceutically acceptable salt of any of the foregoing compounds.

10. Use of a compound of formula (I) as defined in any one of claims 1 to 9 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of anxiety or depression in mammals.

11. A process for the preparation a pharmaceutical composition which process comprises admixing a compound of formula (I), as defined in claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Patentansprüche
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, GR, IT, LI, LU, NL, SE

1. Verbindung der Formel (I) oder ein pharmazeutisch verträgliches Salz davon:



(I)

in der:

R_1 ein Wasserstoffatom oder ein C_{1-6}-Alkyl-, C_{3-6}-Cycloalkyl-, C_{3-6}-Cycloalkyl-C_{1-4}-alkyl-, C_{2-6}-Alkenyl- oder C_{2-6}-Alkinylrest ist;
R_2, R_3 und R_4 unabhängig gewählt werden aus: einem Wasserstoffatom, einem C_{1-6}-Alkyl-, C_{1-6}-Alkoxy-, C_{1-6}-Alkoxycarbonyl-, C_{1-6}-Alkylthio-, Hydroxy-und C_{2-7}-Alkanoylrest, einem Chlor- und Fluoratom, einem Trifluormethyl, Nitro-, mit einem oder zwei C_{1-6}-Alkyl- oder mit C_{2-7}-Alkanoylresten gegebenenfalls substituierten Aminorest, einem Cyano-, Carbamoyl- und Carboxyrest und einem Phenyl-, Phenyl-C_{1-4}-alkyl- oder Phenyl-C_{1-4}-alkoxyrest, in denen eine Phenyleinheit gegebenenfalls durch eine dieser Gruppen substituiert ist;
R_5 und R_6 unabhängig gewählt werden aus: einem Wasserstoffatom, einem C_{1-6}-Alkyl-, C_{3-7}-Cycloalkyl-, C_{3-7}-Cycloalkyl-C_{1-4}-alkyl-, C_{2-6}-Alkenyl-, C_{1-7}-Alkanoyl-,C_{1-6}-Alkylsulfonyl-, Di-(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-, 3-Oxobutyl-, 3-Hydroxybutylrest, einem Phenyl-, Phenyl-C_{1-4}-alkyl-, Benzoyl-, Phenyl-C_{2-7}-alkanoyl- oder Benzolsulfonylrest, von denen eine Phenyleinheit gegebenenfalls durch ein oder zwei Halogenatome, C_{1-6}-Alkyl-, C_{1-6}-Alkoxy-, CF_3-, Amino-oder Carboxyreste substituiert ist, oder R_5 und R_6 zusammen einen C_{2-6}-Polymethylenrest bilden, gegebenenfalls durch ein Sauerstoffatom oder eine NR_{11}-Gruppe unterbrochen, wobei R_{11} ein Wasserstoffatom oder ein C_{1-6}-Alkylrest, gegebenenfalls mit einer Hydroxygruppe substituiert, ist;
R_7, R_8, R_9 und R_{10} unabhängig gewählt werden aus: einem Wasserstoffatom, einem C_{1-8}-Alkylrest, gegebenenfalls substituiert durch ein oder zwei Hydroxy-, Oxo- oder C_{1-4}-Alkoxyreste, Halogenatome oder CF_3-Reste, einem C_{3-7}-Cycloalkyl-, C_{3-7}-Cycloalkyl-C_{1-4}-alkyl-, C_{2-7}-Alkanoyl-, C_{2-6}-Alkenyl- oder C_{2-6}-Alkinylrest, die gegebenenfalls entweder durch ein, zwei oder drei Halogenatome oder C_{1-4}-Alkylreste substituiert sind, einem C_{3-7}-Cycloalkenylrest, gegebenenfalls durch ein oder zwei Halogenatome oder C_{1-4}-Alkylrestesubstituiert, einem C_{3-7}-Cycloalkenyl-C_{1-4}-alkylrest, in dem der Cycloalkenylring gegebenenfalls durch ein oder zwei Halogenatome oder C_{1-4}-Alkylrestesubstituiert ist, und einem Phenylrest, gegebenenfalls durch ein oder zwei Halogenatome, C_{1-6}-Alkyl-, C_{1-6}-Alkoxy-, CF_3-, Amino- oder Carboxyreste substituiert,
oder R_7 und R_8 zusammen und / oder R_9 und R_{10} zusammen C_{3-6}-Polymethylenreste, gegebenenfalls durch C_{1-6}-Alkyl- oder C_{2-6}-Alkenylreste substituiert, bilden; und
Z der Rest $(CR_{14}R_{15})_n$ ist, wobei n 0, 1 oder 2 ist und R_{14} und R_{15} unabhängig aus einem Wasserstoffatom, C_{1-6}-Alkyl- oder C_{2-6}-Alkenylrest gewählt wird.

2. Verbindung nach Anspruch 1, wobei R_2, R_3 und R_4 Wasserstoffatome sind.

3. Verbindung nach Anspruch 1 oder 2, wobei R_5 ein Wasserstoffatom ist und R_6 ein Wasserstoffatom oder ein C_{1-6}-Alkylrest ist.

4. Verbindung nach einem der Ansprüche 1 bis 3, wobei R_1 ein Wasserstoffatom oder eine Methyl-, Ethyl-, Proyl- oder 2-Propenylgruppe ist.

5. Verbindung nach einem der Ansprüche 1 bis 4, wobei R_7 ein Wasserstoffatom oder eine Methyl- oder Ethylgruppe ist und R_8 ein Wasserstoffatom oder eine Methylgruppe ist.

6. Verbindung nach einem der Ansprüche 1 bis 5, wobei R_9 ein Wasserstoffatom oder eine Methylgruppe ist und R_{10} ein Wasserstoffatom oder eine Methyl-oder Phenylgruppe ist.

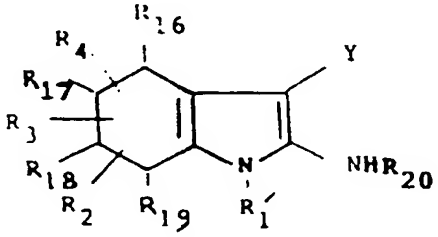
7. Verbindung nach einem der Ansprüche 1 bis 6, wobei n in Z 1 oder 2 ist, R_{14} ein Wasserstoffatom und R_{15} ein Wasserstoffatom oder eine Methylgruppe ist.

8. Verbindung nach einem der Ansprüche 1 bis 7, wobei n in Z 1 ist.

9. 11-Amino-1,2,3,4-terahydro-6H-chinindolin-1-on,
11-Amino-3,3-dimethyl-1,2,3,4-tetrahydro-6H-chinindolin-1-on,
(±)-11-Amino-3-phenyl-1,2,3,4-tetrahydro-6H-chinindolin-1-on,
11-Amino-6-methyl-1,2,3,4-tetrahydro-6H-chinindoin-1-on,
11-Amino-6-ethyl-1,2,3,4-tetrahydro-6H-chinindolin-1-on,
11-Amino-6-n-propyl-1,2,3,4-tetrahydro-6H-chinindolin-1-on,
11-Amino-6-(2-propenyl)-1,2,3,4-tetrahydro-6H-chinindolin-1-on,
11-Amino-1,2,3,4-tetrahydro-3,3,6-trimethyl-6H-chinindolin-1-on,
(±)-11-Amino-6-methyl-3-phenyl-1,2,3,4-tetrahydro-6H-chinindolin-1-on,

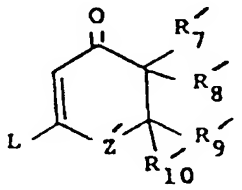
(±)-11-Amino-3,6-dimethyl-1,2,3,4-tetrahydro-6H-chinindolin-1-on,
(±)-11-Amino-2,6-dimethyl-1,2,3,4-tetrahydro-6H-chinindolin-1-on,
(+)-11-Amino-2,6-dimethyl-1,2,3,4-tetrahydro-6H-chinindolin- 1-on,
(-)-11-Amino-2,6-dimethyl-1,2,3,4-tetrahydro-6H-chinindolin-1-on,
(±)-11-Amino-2-ethyl-6-methyl-1,2,3,4-tetrahydro-6H-chinindolin-1-on,
11-Amino-1,2,3,4-tetrahydro-2,2,6-trimethyl-6H-chinindolin-1-on,
(±)-11-Amino-6-methyl-2-(2-propinyl)-1,2,3,4-tetrahydro-6H-chinindolin-1-on,
(±)-11-Amino-1,2,3,4-terahydro-2,4,6-trimethyl-6H-chinindolin-1-on,
12-Amino-7-methy-cyclohepta[5,6]pyrido[2,3-b]indol-1-on,
10-Amino-5-methyl-cyclopenta[5,6]pyrido[2,3-b]indol-1-on oder
(±)-12-Amino-2,7-dimethyl-cyclohepta[5,6]pyrido-[2,3-b]indol-1-on oder ein pharmazeutisch verträgliches Satz einer der vorstehenden Verbindungen.

10. Verfahren zur Herstellung einer Verbindung der Formel (I), wie in Anspruch 1 definiert, oder eines pharmazeutisch verträglichen Salzes davon, umfassend die Kondensation einer Verbindung der Formel (IV):



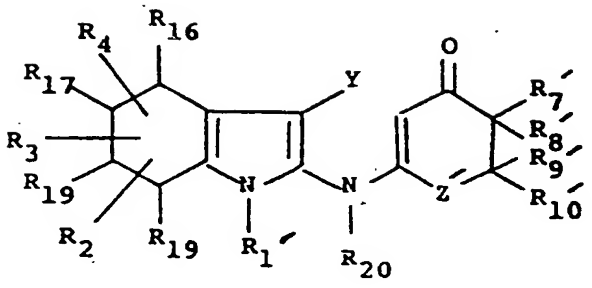
(IV)

mit einer Verbindung der Formel (V):



(V)

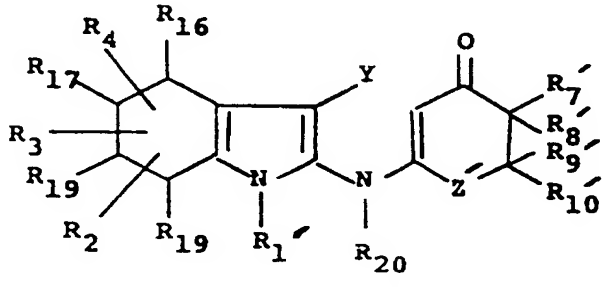
wobei R_1' der Rest R_1, wie in Anspruch 1 definiert, oder eine N-Schutzgruppe ist, R_2, R_3 und R_4 wie in Anspruch 1 definiert sind, R_{16}, R_{17}, R_{18} und R_{19} jeweils Wasserstoffatome sind oder R_{16} und R_{17}, und R_{18} und R_{19} zusammen eine Bindung bilden, L eine Abgangsgruppe ist, Y eine CN- oder COL_1-Gruppe ist, worin L_1 eine Abgangsgruppe ist, R_{20} ein Wasserstoffatom oder eine N-Schutzgruppe ist und R_7', R_8', R_9', R_{10}' und Z' jeweils R_7, R_8, R_9, R_{10} bzw. Z, wie in Anspruch 1 definiert, oder eine in R_7, R_8, R_9, R_{10} bzw. Z umwandelbare Gruppen sind, um ein acyclisches Enamin-Zwischenprodukt der Formel (VI) zu liefern:



(VI)

wobei Y, R_1', R_2, R_3, R_4, R_{16}, R_{17}, R_{18}, R_{19} und R_{20} wie in Formel (IV) definiert sind und R_7', R_8', R_9', R_{10}' und Z' wie in Formel (V) definiert sind; und danach, gegebenenfalls oder falls notwendig und in jeder geeigneten Abfolge, Cyclisierung der Enamin-Zwischenstufe, Enantiomerenspaltung, Umwandlung von R_{20}, wenn es ein Wasserstoffatom ist, in eine N-Schutzgruppe, Umwandlung von R_7', R_8', R_9', R_{10}' und Z' in R_7, R_8, R_9, R_{10} bzw. Z, wenn Y eine COL_1-Gruppe ist, Umwandlung der so erhaltenen Hydroxygruppe in eine Abgangsgruppe und Umsetzung letzterer mit einer Verbindung HNR_5R_6, Entfernung aller H-Schutzgruppen an R_1', Entfernen aller N-Schutzgruppen an R_{20}, Umwandlung von R_{16}, R_{17}, R_{18} und R_{19}, wenn diese Wasserstoffatome sind, in zwei Bindungen, gegenseitige Umwandlung von R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10} oder Z und / oder Erzeugung eines pharmazeutisch verträglichen Salzes der Verbindung der Formel (I).

11. Verbindung der Formel (VI) oder ein Salz davon:

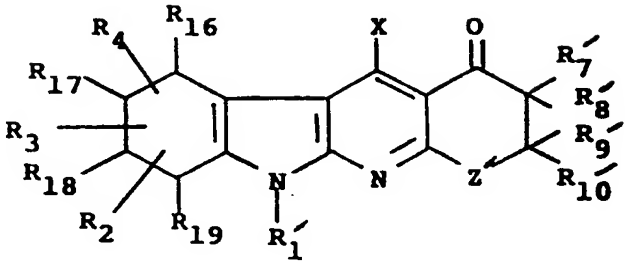


(VI)

wobei Y, R_1', R_2, R_3, R_4, R_7', R_8', R_9', R_{10}', R_{16}, R_{17}, R_{18}, R_{19}, R_{20} und Z wie in Anspruch 10 definiert sind.

12. 1-(4-Methoxyphenyl)methyl-2-[(3-oxo-1-cyclohexen-1-yl)amino]-4,5,6,7-tetrahydro-1H-indol-3-carbonitril,
2-[(5,5-Dimethyl-3-oxo-1-cyclohexen-1-yl)amino]-1-(4-methoxyphenyl)methyl-4,5,6,7-tetrahydro-1H-indol-3-carbonitril,
(±)-2-[(5-Methyl-3-oxo-1-cyclohexen-1-yl)amino]-1-methyl-1H-indol-3-carbonitril,
(±)-2-[(4-Methyl-3-oxo-1-cyclohexen-1-yl)amino]-1-methyl-1H-indol-3-carbonitril,
(±)-2-[(4-Ethyl-3-oxo-1-cyclohexen-1-yl)amino]-1-methyl-1H-indol-3-carbonitril,
2-[(4,4-Dimethyl-3-oxo-1-cyclohexen-1-yl)amino]-1-methyl-1H-indol-3-carbonitril,
1-Methyl-2-[(3-oxo-1-cyclopenten-1-yl)amino]-1H-indol-3-carbonitril,
1-Methyl-2-[(3-oxo-1-cyclohepten-1-yl)amino]-1H-indol-3-carbonitril,
1-Methyl-2-[(3-oxo-1-cyclohexen-1-yl)amino]-1H-indol-3-carbonitril.

13. Verbindung der Formel (VII) oder ein Salz davon:



(VII)

wobei X eine NH_2- oder OH-Gruppe oder ein Chloratom ist, R_1', R_2, R_3, R_4, R_7', R_8', R_9', R_{10}', R_{16}, R_{17}, R_{18}, R_{19} und Z' wie in Anspruch 10 definiert sind, mit der Maßgabe, daß X keine NH_2-Gruppe ist, wenn R_1', R_7', R_8', R_9', R_{10}' und Z' wie R_1, R_7, R_8, R_9, R_{10} und Z in Anspruch 1 definiert sind und R_{16} und R_{17}, und R_{18} und R_{19} zusammen eine Bindung bilden.

14. 11-Amino-6-(4-methoxyphenyl)methyl-1,2,3,4,7,8,9,10-octahydro-6H-chinindolin-1-on,
11-Amino-3,3-dimethyl-6-(4-methoxyphenyl)methyl-1,2,3,4,7,8,9,10-octahydro-6H-chinindolin-1-on,
(±)-11-Amino-6-(4-methoxyphenyl)methyl-1,2,3,4,7,8,9,10-octahydro-3-phenyl-6H-chinindolin-1-on,
11-Amino-6-(4-methoxyphenyl)methyl-1,2,3,4-tetrahydro-6H-chinindolin-1-on,
11-Amino-3,3-dimethyl-6-(4-methoxyphenyl)methyl-1,2,3,4-tetrahydro-6H-chinindolin-1-on oder
(±)-11-Amino-6-(4-methoxyphenyl)methyl-3-phenyl-1,2,3,4-tetrahydro-6H-chinindolin-1-on.

15. Arzneimittel, umfassend eine Verbindung nach einem der Ansprüche 1 bis 9 und einen pharmazeutisch verträglichen Träger.

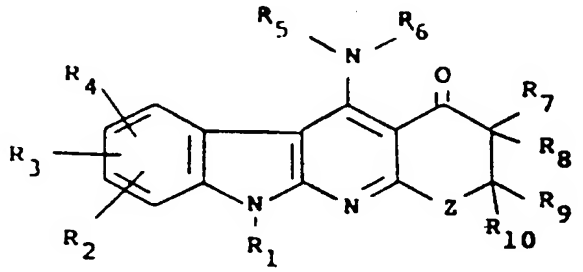
16. Verbindung nach einem der Ansprüche 1 bis 9 zur Verwendung als therapeutischen Wirkstoff.

17. Verbindung nach einem der Ansprüche 1 bis 9, zur Verwendung in der Behandlung von Angst oder Depression bei Säugern.

18. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 9 zur Herstellung eines Medikaments zur Behandlung von Angst oder Depression bei Säugern.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung einer Verbindung der Formel (I) oder eines pharmazeutisch verträglichen Salzes davon:



(I)

in der:
R_1 ein Wasserstoffatom oder ein C_{1-6}-Alkyl-, C_{3-6}-Cycloalkyl-, C_{3-6}-Cycloalkyl-C_{1-4}-alkyl-, C_{2-6}-Alkenyl- oder C_{2-6}-Alkinylrest ist;
R_2, R_3 und R_4 unabhängig ausgewählt werden aus: einem Wasserstoffatom, einem C_{1-6}-Alkyl-, C_{1-6}-

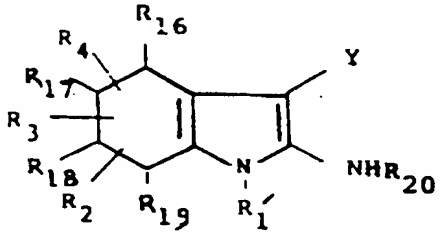
Alkoxy-, C_{1-6}-Alkoxycarbonyl-, C_{1-6}-Alkylthio-, Hydroxy-und C_{2-7}-Alkanoylrest, einem Chlor- und Fluoratom, einem Trifluormethyl-, Nitro-, mit einem oder zwei C_{1-6}-Alkyl- oder mit C_{2-7}-Alkanoylresten gegebenenfalls substituierten Aminorest, einem Cyano-, Carbamoyl- und Carboxyrest und einem Phenyl-, Phenyl-C_{1-4}-alkyl- oder Phenyl-C_{1-4}-alkoxyrest, in denen eine Phenyleinheit gegebenenfalls durch eine dieser Gruppen substituiert ist;

R_5 und R_6 unabhängig gewählt werden aus: einem Wasserstoffatom, einem C_{1-6}-Alkyl-, C_{3-7}-Cycloalkyl-, C_{3-7}-Cycloalkyl-C_{1-4}-alkyl-, C_{2-6}-Alkenyl-, C_{1-7}-Alkanoyl-,C_{1-6}-Alkylsulfonyl-, Di-(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-, 3-Oxobutyl-, 3-Hydroxybutylrest, einem Phenyl-, Phenyl-C_{1-4}-alkyl-, Benzoyl-, Phenyl-C_{2-7}-alkanoyl- oder Benzolsulfonylrest, von denen eine Phenyleinheit gegebenenfalls durch ein oder zwei Halogenatome, C_{1-6}-Alkyl-, C_{1-6}-Alkoxy-, CF_3-, Amino-oder Carboxyreste substituiert ist, oder R_5 und R_6 zusammen einen C_{2-6}-Polymethylenrest bilden, gegebenenfalls durch ein Sauerstoffatom oder eine NR_{11}-Gruppe unterbrochen, wobei R_{11} ein Wasserstoffatom oder ein C_{1-6}-Alkylrest, gegebenenfalls mit einer Hydroxygruppe substituiert, ist;

R_7, R_8, R_9 und R_{10} unabhängig gewählt werden aus: einem Wasserstoffatom, einem C_{1-8}-Alkylrest, gegebenenfalls substituiert durch ein oder zwei Hydroxy-, Oxo- oder C_{1-4}-Alkoxyreste, Halogenatome oder CF_3-Reste, einem C_{3-7}-Cycloalkyl-, C_{3-7}-Cycloalkyl-C_{1-4}-alkyl-, C_{2-7}-Alkanoyl-, C_{2-6}-Alkenyl- oder C_{2-6}-Alkinylrest, die gegebenenfalls entweder durch ein, zwei oder drei Halogenatome oder C_{1-4}-Alkylreste substituiert sind, einem C_{3-7}-Cycloalkenylrest, gegebenenfalls durch ein oder zwei Halogenatome oder C_{1-4}-Alkylrestesubstituiert, einem C_{3-7}-Cycloalkenyl-C_{1-4}-alkylrest, in dem der Cycloalkenylring gegebenenfalls durch ein oder zwei Halogenatome oder C_{1-4}-Alkylrestesubstituiert ist, und einem Phenylrest, gegebenenfalls durch ein oder zwei Halogenatome, C_{1-6}-Alkyl-, C_{1-6}-Alkoxy-, CF_3-, Amino- oder Carboxyreste substituiert,

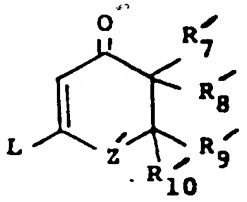
oder R_7 und R_8 zusammen und / oder R_9 und R_{10} zusammen C_{3-6}-Polymethylenreste, gegebenenfalls durch C_{1-6}-Alkyl- oder C_{2-6}-Alkenylreste substituiert, bilden; und

Z der Rest $(CR_{14}R_{15})_n$ ist, wobei n 0, 1 oder 2 ist und R_{14} und R_{15} unabhängig aus einem Wasserstoffatom, C_{1-6}-Alkyl- oder C_{2-6}-Alkenylrest gewählt wird, umfassend die Kondensation einer Verbindung der Formel (IV):



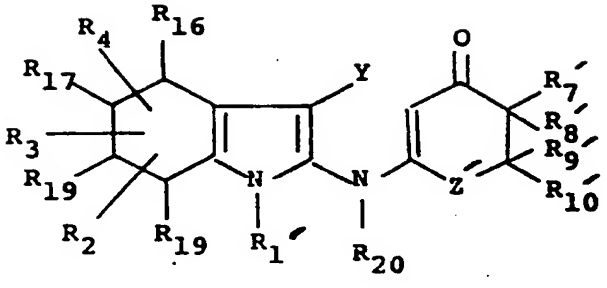
(IV)

mit einer Verbindung der Formel (V):



(V)

wobei R_1' der Rest R_1, wie in Anspruch 1 definiert, oder eine N-Schutzgruppe ist, R_2, R_3 und R_4 wie in Anspruch 1 definiert sind, R_{16}, R_{17}, R_{18} und R_{19} jeweils Wasserstoffatome sind oder R_{16} und R_{17}, und R_{18} und R_{19} zusammen eine Bindung bilden, L eine Abgangsgruppe ist, Y eine CN- oder COL_1-Gruppe ist, worin L_1 eine Abgangsgruppe ist, R_{20} ein Wasserstoffatom oder eine N-Schutzgruppe ist und R_7', R_8', R_9', R_{10}' und Z' jeweils R_7, R_8, R_9, R_{10} bzw. Z, wie in Anspruch 1 definiert, oder in R_7, R_8, R_9, R_{10} bzw. Z umwandelbare Gruppen sind, um ein acyclisches Enamin-Zwischenprodukt der Formel (VI) zu liefern:



(VI)

wobei Y, R_1', R_2, R_3, R_4, R_{16}, R_{17}, R_{18}, R_{19} und R_{20} wie in Formel (IV) definiert sind und R_7', R_8', R_9', R_{10}' und Z' wie in Formel (V) definiert sind; und danach, gegebenenfalls oder falls notwendig und in jeder geeigneten Abfolge, Cyclisierung der Enamin-Zwischenstufe, Enantiomerenspaltung, Umwandlung von R_{20}, wenn es ein Wasserstoffatom ist, in eine N-Schutzgruppe, Umwandlung von R_7', R_8', R_9', R_{10}' und Z' in R_7, R_8, R_9, R_{10} bzw. Z, wenn Y eine COL_1-Gruppe ist, Umwandlung der so erhaltenen Hydroxygruppe in eine Abgangsgruppe und Umsetzung letzterer mit einer Verbindung HNR_5R_6, Entfernung aller N-Schutzgruppen an R_1', Entfernen aller N-Schutzgruppen an R_{20}, Umwandlung von R_{16}, R_{17}, R_{18} und R_{19}, wenn diese Wasserstoffatome sind, in zwei Bindungen, gegenseitige Umwandlung von R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10} oder Z und / oder Erzeugung eines pharmazeutisch verträglichen Salzes der Verbindung der Formel (I).

2. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel (I), wie in Anspruch 1 definiert, oder eines pharmazeutisch verträglichen Salzes davon, wobei R_2, R_3 und R_4 Wasserstoffatome sind.

3. Verfahren nach den Ansprüchen 1 oder 2 zur Herstellung einer Verbindung der Formel (I), wie in Anspruch 1 definiert, oder eines pharmazeutisch verträglichen Salzes davon, wobei R_5 ein Wasserstoffatom und R_6 ein Wasserstoffatom oder C_{1-6}-Alkylrest ist.

4. Verfahren nach einem der Ansprüche 1 bis 3 zur Herstellung einer Verbindung der Formel (I), wie in Anspruch 1 definiert, oder eines pharmazeutisch verträglichen Salzes davon, wobei R_1 ein Wasserstoffatom oder eine Methyl-, Ethyl-, Propyl- oder 2-Propenylgruppe ist.

5. Verfahren nach einem der Ansprüche 1 bis 4 zur Herstellung einer Verbindung der Formel (I), wie in Anspruch 1 definiert, oder eines pharmazeutisch verträglichen Salzes davon, wobei R_7 ein Wasserstoffatom oder eine Methyl-oder Ethylgruppe ist und R_8 ein Wasserstoffatom oder eine Methylgruppe ist.

6. Verfahren nach einem der Ansprüche 1 bis 5 zur Herstellung einer Verbindung der Formel (I), wie in Anspruch 1 definiert, oder eines pharmazeutisch verträglichen Salzes davon, wobei R_9 ein Wasserstoffatom oder eine Methylgruppe und R_{10} ein Wasserstoffatom, eine Methyl- oder Phenylgruppe ist.

7. Verfahren nach einem der Ansprüche 1 bis 6 zur Herstellung einer Verbindung der Formel (I), wie in Anspruch 1 definiert, oder eines pharmazeutisch verträglichen Salzes davon, wobei n in Z 1 oder 2 ist, R_{15} ein Wasserstoffatom und R_{16} ein Wasserstoffatom oder eine Methylgruppe ist.

8. Verfahren nach einem der Ansprüche 1 bis 7 zur Herstellung einer Verbindung der Formel (I), wie in Anspruch 1 definiert, oder eines pharmazeutisch verträglichen Salzes davon, wobei n in Z 1 ist.

9. Verfahren nach einem der Ansprüche 1 bis 7 zur Herstellung einer Verbindung der Formel (I), nämlich:
11-Amino-1,2,3,4-terahydro-6H-chinindolin-1-on,
11-Amino-3,3-dimethyl-1,2,3,4-tetrahydro-6H-chinindolin-1-on,
(±)-11-Amino-3-phenyl-1,2,3,4-tetrahydro-6H-chinindolin-1-on,
11-Amino-6-methyl-1,2,3,4-tetrahydro-6H-chinindolin-1-on,
11-Amino-6-ethyl-1,2,3,4-tetrahydro-6H-chinindolin-1-on,
11-Amino-6-n-propyl-1,2,3,4-tetrahydro-6H-chinindolin-1-on,

11-Amino-6-(2-propenyl)-1,2,3,4-tetrahydro-6H-chinindolin-1-on,
11-Amino-1,2,3,4-tetrahydro-3,3,6-trimethyl-6H-chinindolin-1-on,
(±)-11-Amino-6-methyl-3-phenyl-1,2,3,4-tetrahydro-6H-chinindolin-1-on,
(±)-11-Amino-3,6-dimethyl-1,2,3,4-tetrahydro-6H-chinindolin-1-on,
(±)-11-Amino-2,6-dimethyl-1,2,3,4-tetrahydro-6H-chinindolin-1-on,
(+)-11-Amino-2,6-dimethyl-1,2,3,4-tetrahydro-6H-chinindolin-1-on,
(-)-11-Amino-2,6-dimethyl-1,2,3,4-tetrahydro-6H-chinindolin-1-on,
(±)-11-Amino-2-ethyl-6-methyl-1,2,3,4-tetrahydro-6H-chinindolin-1-on,
11-Amino-1,2,3,4-tetrahydro-2,2,6-trimethyl-6H-chinindolin-1-on,
(±)-11-Amino-6-methyl-2-(2-propinyl)-1,2,3,4-tetrahydro-6H-chinindolin-1-on,
(±)-11-Amino-1,2,3,4-terahydro-2,4,6-trimethyl-6H-chinindolin-1-on,
12-Amino-7-methyl-cyclohepta[5,6]pyrido[2,3-b]indol-1-on,
10-Amino-5-methyl-cyclopenta[5,6]pyrido[2,3-b]indol-1-on oder
(±)-12-Amino-2,7-dimethyl-cyclohepta[5,6]pyrido-[2,3-b]indol-1-on oder ein pharmazeutisch verträgliches Salz von einer der vorstehenden Verbindungen.

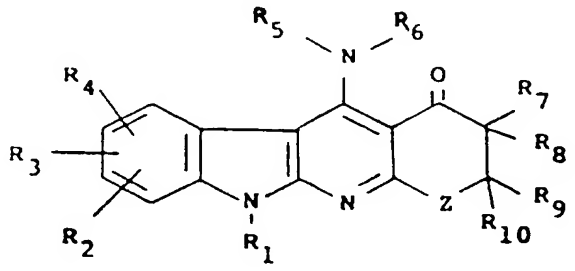
10. Verwendung einer Verbindung der Formel (I), wie in einem der Ansprüche 1 bis 9 definiert, oder eines pharmazeutisch verträglichen Salzes davon, zur Herstellung eines Medikaments zur Behandlung von Angst oder Depression bei Säugern.

11. Verfahren zur Herstellung eines Arzneimittels, umfassend das Vermischen einer Verbindung der Formel (I), wie in Anspruch 1 definiert, oder eines pharmazeutisch verträgliches Salzes davon mit einem pharmazeutisch verträglichen Träger.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, GR, IT, LI, LU, NL, SE

1. Composé de formule (I) ou sel de celui-ci acceptable du point de vue pharmaceutique :



(I)

dans laquelle :

R_1 est un atome d'hydrogène, un groupe alkyle en C_{1-6}, cycloalkyle en C_{3-6}, cycloalkyl-(en C_{3-6})-alkyle en C_{1-4}, alcényle en C_{2-6} ou alcynyle en C_{2-6};

R_2, R_3 et R_4 sont indépendamment choisis parmi un atome d'hydrogène, un groupe alkyle en C_{1-6}, alcoxy en C_{1-6}, alcoxycarbonyle en C_{1-6}, alkylthio en C_{1-6}, hydroxy, alcanoyle en C_{2-7}, un atome de chlore, de fluor, un groupe trifluorométhyle, nitro, amino éventuellement substitué par un ou deux groupes alkyles en C_{1-6} ou par un groupe alcanoyle en C_{2-7}, cyano, carbamoyle et carboxy, et un groupe phényle, phényl-alkyle en C_{1-4} ou phényl-alcoxy en C_{1-4} où une quelconque partie phényle est éventuellement substituée par l'un quelconque de ces groupes;

R_5 et R_6 sont indépendamment choisis parmi un atome d'hydrogène, un groupe alkyle en C_{1-6}, cycloalkyle en C_{3-7}, cycloalkyle-(en C_{3-7})-alkyle C_{1-4}, alcényle en C_{2-6}, alcanoyle en C_{1-7}, alkylsulfonyle en C_{1-6}, dialkyl-(en C_{1-6})-aminoalkyle en C_{1-6}, 3-oxobutyle, 3-hydroxybutyle, et phényle, phényl-alkyle en C_{1-4}, benzoyle, phényl-alcanoyle en C_{2-7} ou benzènesulfonyle, de quelconques parties phényles de ceux-ci étant éventuellement substituées par un ou deux

atomes d'halogène, groupes alkyles en C_{1-6}, alcoxy en C_{1-6}, CF_3, amino ou carboxy, ou bien R_5 et R_6 forment ensemble un radical polyméthylène en C_{2-6} éventuellement interrompu par de l'oxygène ou NR_{11}, où R_{11} est un atome d'hydrogène ou un groupe alkyle en C_{1-6} éventuellement substitué par un groupe hydroxy;

R_7, R_8, R_9 et R_{10} sont indépendamment choisis parmi un atome d'hydrogène, un groupe alkyle en C_{1-8} éventuellement substitué par un ou deux groupes hydroxy, oxo, alcoxy en C_{1-4}, un atome d'halogène ou des groupes CF_3, cycloalkyle en C_{3-7}, cycloalkyl-(en C_{3-7})-alkyle C_{1-4}, alcanoyle en C_{2-7}, alcényle en C_{2-6} ou alcynyle en C_{2-6}, l'un ou l'autre étant éventuellement substitué par un, deux ou trois atomes d'halogène ou groupes alkyle en C_{1-4}, cycloalcényle en C_{3-7} éventuellement substitué par un ou deux atomes d'halogène ou groupes alkyles en C_{1-4}, cycloalcènyl-(en C_{3-7})-alkyle en C_{1-4}, où le cycle cycloalcényle est éventuellement substitué par un ou deux atomes d'halogène ou groupe alkyles en C_{1-4}, et phényle éventuellement substitué par un ou deux atomes d'halogène, groupes alkyle en C_{1-6}, alcoxy en C_{1-6}, CF_3, amino ou carboxy,

ou bien R_7 et R_8 ensemble et/ou R_9 et R_{10} ensemble forment un radical polyméthylène en C_{3-6} éventuellement substitué par un groupe alkyle en C_{1-6} ou alcényle en C_{2-6}; et

Z est un groupe $(CR_{14}R_{15})_n$, dans lequel n est 0, 1 ou 2 et R_{14} et R_{15} sont indépendamment choisis parmi un atome d'hydrogène, un groupe alkyle en C_{1-6} ou alcényle en C_{2-6}.

2. Composé suivant la revendication 1, dans lequel R_2, R_3 et R_4 sont un atome d'hydrogène.

3. Composé suivant les revendications 1 ou 2, dans lequel R_5 est un atome d'hydrogène et R_6 est un atome d'hydrogène ou un groupe alkyle en C_{1-6}.

4. Composé suivant l'une quelconque des revendications 1 à 3, dans lequel R_1 est un atome d'hydrogène, un groupe méthyle, éthyle, propyle ou prop-2-ènyle.

5. Composé suivant l'une quelconque des revendications 1 à 4, dans lequel R_7 est un atome d'hydrogène, un groupe méthyle ou éthyle et R_8 est un atome d'hydrogène ou un groupe méthyle.

6. Composé suivant l'une quelconque des revendications 1 à 5, dans lequel R_9 est un atome d'hydrogène ou un groupe méthyle et R_{10} est un atome d'hydrogène, un groupe méthyle ou phényle.

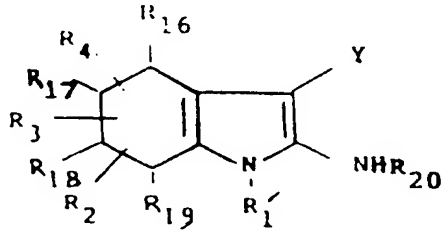
7. Composé suivant l'une quelconque des revendications 1 à 6, dans lequel n dans Z est 1 ou 2, R_{14} est un atome d'hydrogène et R_{15} est un atome d'hydrogène ou un groupe méthyle.

8. Composé suivant l'une quelconque des revendications 1 à 7, dans lequel n dans Z est 1.

9. Composé suivant la revendication 1, comprenant les composés suivants:
11-amino-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
11-amino-3,3-diméthyl-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
(±)-11-amino-3-phényl-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
11-amino-6-méthyl-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
11-amino-6-éthyl-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
11-amino-6-n-propyl-1,2,3,4-tétrahydro-6H-quinindolin- 1-one,
11-amino-6-(2-propényl)-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
11-amino-1,2,3,4-tétrahydro-3,3,6-triméthyl-6H-quinindolin-1-one,
(±)-11-amino-6-méthyl-3-phényl-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
(±)-11-amino-3,6-diméthyl-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
(±)-11-amino-2,6-diméthyl-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
(+)-11-amino-2,6-diméthyl-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
(-)-11-amino-2,6-diméthyl-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
(±)-11-amino-2-éthyl-6-méthyl-1,2,3,4-tétrahydro-6H-quinindolin-1-one,

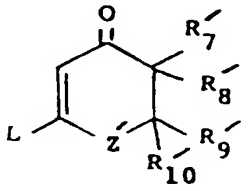
11-amino-1,2,3,4-tétrahydro-2,2,6-triméthyl-6H-quinindolin-1-one,
(±)-11-amino-6-méthyl-2-(2-propynyl)-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
(±)-11-amino-1,2,3,4-tétrahydro-2,4,6-triméthyl-6H-quinindolin-1-one,
12-amino-7-méthyl-cyclohepta-[5,6]-pyrido-[2,3-b]-indol-1-one,
10-amino-5-méthyl-cyclopenta-[5,6]-pyrido-[2,3-b]-indol-1-one ou
(±)-12-amino-2,7-diméthyl-cyclohepta-[5,6]-pyrido-[2,3-b]-indol-1-one,
ou sel de l'un quelconque de ces composés acceptables du point de vue pharmaceutique.

10. Procédé pour la préparation d'un composé de formule (I) suivant la revendication 1, ou d'un sel de celui-ci acceptable du point de vue pharmaceutique, qui comprend la condensation d'un composé de formule (IV) :



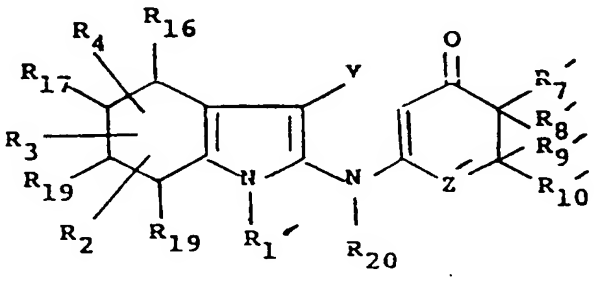
(IV)

avec un composé de formule (V) :



(V)

dans laquelle R_1' est R_1 tel que défini dans la revendication 1 ou un groupe N-protecteur, R_2, R_3 et R_4 sont tels que définis dans la revendication 1, R_{16}, R_{17}, R_{18} et R_{19} sont chacun un atome d'hydrogène ou bien R_{16} et R_{17}, et R_{18} et R_{19} représentent ensemble une liaison, L est un groupe mobile, Y est un groupe CN ou COL_1, où L_1 est un groupe mobile, R_{20} est un atome d'hydrogène ou un groupe N-protecteur et R_7', R_8', R_9', R_{10}' et Z' sont R_7, R_8, R_9, R_{10} et Z respectivement, tels que définis dans la revendication 1 ou un groupe pouvant être converti en R_7, R_8, R_9, R_{10} et Z respectivement, pour donner un intermédiaire énamine acyclique de formule (VI) :

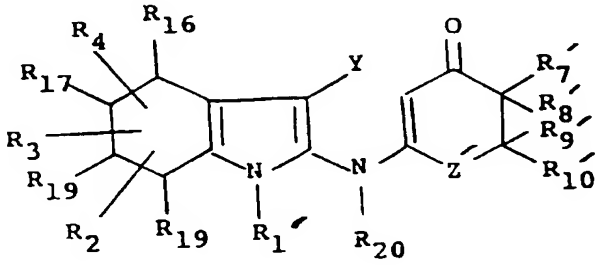


(VI)

dans laquelle Y, R_1', R_2, R_3, R_4, R_{16}, R_{17}, R_{18}, R_{19} et R_{20} sont tels que définis dans la formule (IV) et R_7', R_8', R_9', R_{10}' et Z' sont tels que définis dans la formule (V); et ensuite, si cela est désiré ou

nécessaire, et dans un ordre approprié quelconque, la cyclisation de l'intermédiaire ènamine, la séparation de quelconques énantiomères, la conversion de R_{20} lorsqu'il est un atome d'hydrogène en un groupe N-protecteur, la conversion de R_7', R_8', R_9', R_{10}' et Z' en R_7, R_8, R_9, R_{10} et Z respectivement, lorsque Y est un groupe COL_1, la conversion du groupe hydroxy résultant en un groupe mobile et la réaction de ce dernier avec un composé HNR_5R_6, l'élimination d'un quelconque groupe N-protecteur R_1', l'élimination d'un quelconque groupe N-protecteur R_{20}, la conversion de R_{16}, R_{17}, R_{18} et R_{19} lorsqu'ils sont un atome d'hydrogène en deux liaisons, l'interconversion de R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10} ou Z et/ou la formation d'un sel acceptable du point de vue pharmaceutique du composé de formule (I).

11. Composé de formule (VI) ou sel de celui-ci :

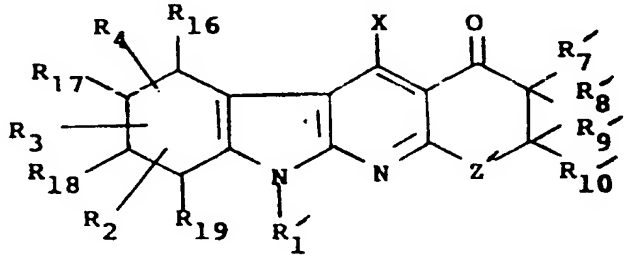


(VI)

dans laquelle Y, R_1', R_2, R_3, R_4, R_7', R_8', R_9', R_{10}', R_{16}, R_{17}, R_{18}, R_{19}, R_{20} et Z sont tels que définis dans la revendication 10.

12. Composés choisis parmi les suivants :
1-(4-méthoxyphényl)-méthyl-2-[(3-oxo-1-cyclohexèn-1-yl)-amino]-4,5,6,7-tétrahydro-1H-indole-3-carbonitrile,
2-[(5,5-diméthyl-3-oxo-1-cyclohexèn-1-yl)-amino]-1-(4-méthoxyphényl)méthyl-4,5,6,7-tétrahydro-1H-indole-3-carbonitrile,
(±)-2-[(5-méthyl-3-oxo-1-cyclohexèn-1-yl)-amino]-1-méthyl-1H-indole-3-carbonitrile,
(±)-2-[(4-méthyl-3-oxo-1-cyclohexèn-1-yl)-amino]-1-méthyl-1H-indole-3-carbonitrile,
(±)-2-[(4-éthyl-3-oxo-1-cyclohexèn-1-yl)-amino]-1-méthyl-1H-indole-3-carbonitrile,
2-[(4,4-diméthyl-3-oxo-1-cyclohexèn-1-yl)-amino]-1-méthyl-1H-indole-3-carbonitrile,
1-méthyl-2-[(3-oxo-1-cyclopentèn-1-yl)-amino]-1H-indole-3-carbonitrile,
1-méthyl-2-[(3-oxo-1-cycloheptèn-1-yl)-amino]-1H-indole-3-carbonitrile ou
1-méthyl-2-[(3-oxo-1-cyclohexèn-1-yl)-amino]-1H-indole-3-carbonitrile.

13. Composé de formule (VII) ou sel de celui-ci :



(VII)

dans laquelle X est NH_2, OH ou un atome de chlore, R_1', R_2, R_3, R_4, R_7', R_8', R_9', R_{10}', R_{16}, R_{17}, R_{18}, R_{19} et Z' sont tels que définis dans la revendication 10, à condition que, lorsque R_1', R_7', R_8', R_9', R_{10}' et Z' sont R_1, R_7, R_8, R_9, R_{10} et Z tels que définis dans la revendication 1 et que R_{16} et R_{17} ainsi que R_{18} et R_{19} représentent ensemble une liaison, X ne soit pas NH_2.

14. Composés choisis parmi les suivants :
11-amino-6-(4-méthoxyphényl)-méthyl-1,2,3,4,7,8,9,10-octahydro-6H-quinindolin-1-one,
11-amino-3,3-diméthyl-6-(4-méthoxyphényl)-méthyl-1,2,3,4,7,8,9,10-octahydro-6H-quinindolin-1-one,
(±)-11-amino-6-(4-méthoxyphényl)-méthyl-1,2,3,4,7,8,9,10-octahydro-3-phényl-6H-quinindolin-1-one,
11-amino-6-(4-méthoxyphényl)-méthyl-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
11-amino-3,3-diméthyl-6-(4-méthoxyphényl)-méthyl-1,2,3,4-tétrahydro-6H-quinindolin-1-one ou
(±)-11-amino-6-(4-méthoxyphényl)-méthyl-3-phényl-1,2,3,4-tétrahydro-6H-quinindolin-1-one.

15. Composition pharmaceutique qui comprend un composé suivant l'une quelconque des revendications 1 à 9 et un support acceptable du point de vue pharmaceutique.

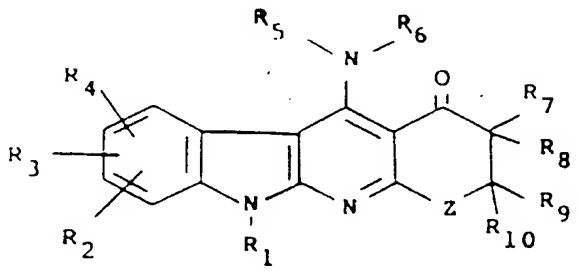
16. Composé suivant l'une quelconque des revendications 1 à 9, utile en tant que substance thérapeutique active.

17. Composé suivant l'une quelconque des revendications 1 à 9, utile dans le traitement de l'anxiété ou de la dépression chez les mammifères.

18. Utilisation d'un composé suivant l'une quelconque des revendications 1 à 9, dans la fabrication d'un médicament pour le traitement de l'anxiété ou la dépression chez les mammifères.

Revendications pour l'Etat contractant suivant : ES

1. Procédé pour la préparation d'un composé de formule (I) ou d'un sel de celui-ci acceptable du point de vue pharmaceutique :



(I)

dans laquelle :

R_1 est un atome d'hydrogène, un groupe alkyle en C_{1-6}, cycloalkyle en C_{3-6}, cycloalkyl-(en C_{3-6})-alkyle en C_{1-4}, alcényle en C_{2-6} ou alcynyle en C_{2-6};

R_2, R_3 et R_4 sont indépendamment choisis parmi un atome d'hydrogène, un groupe alkyle en C_{1-6}, alcoxy en C_{1-6}, alcoxycarbonyle en C_{1-6}, alkylthio en C_{1-6}, hydroxy, alcanoyle en C_{2-7}, un atome de chlore, de fluor, un groupe trifluorométhyle, nitro, amino éventuellement substitué par un ou deux groupes alkyles en C_{1-6} ou par un groupe alcanoyle en C_{2-7}, cyano, carbamoyle et carboxy, et un groupe phényle, phényl-alkyle en C_{1-4} ou phényl-alcoxy en C_{1-4} où une quelconque partie phényle est éventuellement substituée par l'un quelconque de ces groupes;

R_5 et R_6 sont indépendamment choisis parmi un atome d'hydrogène, un groupe alkyle en C_{1-6}, cycloalkyle en C_{3-7}, cycloalkyle-(en C_{3-7})-alkyle C_{1-4}, alcényle en C_{2-6}, alcanoyle en C_{1-7}, alkylsulfonyle en C_{1-6}, dialkyl-(en C_{1-6})-aminoalkyle en C_{1-6}, 3-oxobutyle, 3-hydroxybutyle, et phényle, phényl-alkyle en C_{1-4}, benzoyle, phényl-alcanoyle en C_{2-7} ou benzènesulfonyle, de quelconques parties phényles de ceux-ci étant éventuellement substituées par un ou deux atomes d'halogène, groupes alkyles en C_{1-6}, alcoxy en C_{1-6}, CF_3, amino ou carboxy, ou bien R_5 et R_6 forment ensemble un radical polyméthylène en C_{2-6} éventuellement interrompu par de l'oxygène ou NR_{11}, où R_{11} est un atome d'hydrogène ou un groupe alkyle en C_{1-6} éventuellement substitué par

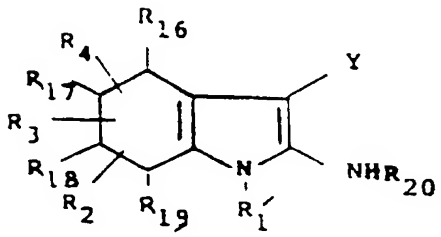
un groupe hydroxy;

R_7, R_8, R_9, et R_{10} sont indépendamment choisis parmi un atome d'hydrogène, un groupe alkyle en C_{1-8} éventuellement substitué par un ou deux groupes hydroxy, oxo, alcoxy en C_{1-4}, un atome d'halogène ou des groupes CF_3, cycloalkyle en C_{3-7}, cycloalkyl-(en C_{3-7},)-alkyle C_{1-4}, alcanoyle en C_{2-7}, alcényle en C_{2-6} ou alcynyle en C_{2-6}, l'un ou l'autre étant éventuellement substitué par un, deux ou trois atomes d'halogène ou groupes alkyle en C_{1-4}, cycloalcényle en C_{3-7} éventuellement substitué par un ou deux atomes d'halogène ou groupes alkyles en C_{1-4}, cycloalcènyl-(en C_{3-7})-alkyle en C_{1-4}, où le cycle cycloalcénylе est éventuellement substitué par un ou deux atomes d'halogène ou groupe alkyles en C_{1-4}, et phényle éventuellement substitué par un ou deux atomes d'halogène, groupes alkyle en C_{1-6}, alcoxy en C_{1-6}, CF_3, amino ou carboxy,

ou bien R_7 et R_8 ensemble et/ou R_9 et R_{10} ensemble forment un radical polyméthylène en C_{3-6} éventuellement substitué par un groupe alkyle en C_{1-6} ou alcényle en C_{2-6}; et

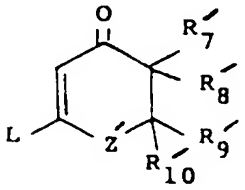
Z est un groupe $(CR_{14}R_{15})_n$, dans lequel n est 0, 1 ou 2 et R_{14} et R_{15} sont indépendamment choisis parmi un atome d'hydrogène, un groupe alkyle en C_{1-6} ou alcényle en C_{2-6},

qui comprend la condensation d'un composé de formule (IV) :



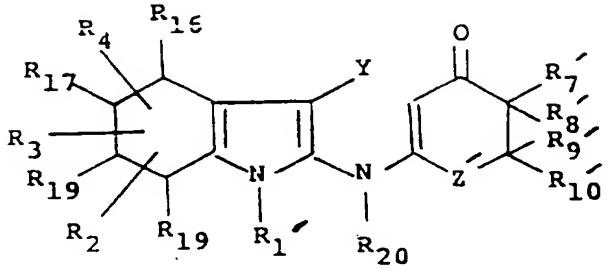
(IV)

avec un composé de formule (V) :



(V)

dans laquelle R_1' est R_1 tel que défini dans la formule (I) ou un groupe N-protecteur, R_2, R_3 et R_4 sont tels que définis dans la formule (I), R_{16}, R_{17}, R_{18} et R_{19} sont chacun un atome d'hydrogène, ou bien R_{16} et R_{17}, et R_{18} et R_{19} représentent ensemble une liaison, L est un groupe mobile, Y est un groupe CN ou COL_1, où L_1 est un groupe mobile, R_{20} est un atome d'hydrogène ou un groupe N-protecteur et R_7', R_8', R_9', R_{10}' et Z' sont R_7, R_8, R_9, R_{10} et Z respectivement, tels que définis dans la formule (I) ou un groupe pouvant être converti en R_7, R_8, R_9, R_{10} et Z respectivement, pour donner un intermédiaire énamine acyclique de formule (VI) :



(VI)

dans laquelle Y, R_1', R_2, R_3, R_4, R_{16}, R_{17}, R_{18}, R_{19} et R_{20} sont tels que définis dans la formule (IV) et R_7', R_8', R_9', R_{10}' et Z' sont tels que définis dans la formule (V); et ensuite, si cela est désiré ou nécessaire, et dans un ordre approprié quelconque, la cyclisation de l'intermédiaire ènamine, la séparation de quelconques énantiomères, la conversion de R_{20} lorsqu'il est un atome d'hydrogène en un groupe N-protecteur, la conversion de R_7', R_8', R_9', R_{10}' et Z' en R_7, R_8, R_9, R_{10} et Z respectivement, lorsque Y est un groupe COL_1, la conversion du groupe hydroxy résultant en un groupe mobile et la réaction de ce dernier avec un composé HNR_5R_6, l'élimination d'un quelconque groupe N-protecteur R_1', l'élimination d'un quelconque groupe N-protecteur R_{20}, la conversion de R_{16}, R_{17}, R_{18} et R_{19} lorsqu'ils sont un atome d'hydrogène en deux liaisons, l'interconversion de R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10} ou Z et/ou la formation d'un sel acceptable du point de vue pharmaceutique du composé de formule (I).

2. Procédé suivant la revendication 1, pour la préparation d'un composé de formule (I) suivant la revendication 1 ou d'un sel de celui-ci acceptable du point de vue pharmaceutique, dans lequel R_2, R_3 et R_4 sont chacun un atome d'hydrogène.

3. Procédé suivant les revendications 1 ou 2, pour la préparation d'un composé de formule (I) suivant la revendication 1 ou d'un sel de celui-ci acceptable du point de vue pharmaceutique, dans lequel R_5 est un atome d'hydrogène et R_6 est un atome d'hydrogène ou un groupe alkyle en C_{1-6}.

4. Procédé suivant l'une quelconque des revendications 1 à 3, pour la préparation d'un composé de formule (I) suivant la revendication 1 ou d'un sel de celui-ci acceptable du point de vue pharmaceutique, dans lequel R_1 est un atome d'hydrogène, un groupe méthyle, éthyle, propyle ou prop-2-ènyle.

5. Procédé suivant l'une quelconque des revendications 1 à 4, pour la préparation d'un composé de formule (I) suivant la revendication 1 ou d'un sel de celui-ci acceptable du point de vue pharmaceutique, dans lequel R_7 est un atome d'hydrogène, un groupe méthyle ou éthyle et R_8 est un atome d'hydrogène ou un groupe méthyle.

6. Procéde suivant l'une quelconque des revendications 1 à 5, pour la préparation d'un composé de formule (I) suivant la revendication 1 ou d'un sel de celui-ci acceptable du point de vue pharmaceutique, dans lequel R_9 est un atome d'hydrogène ou un groupe méthyle et R_{10} est un atome d'hydrogène, un groupe méthyle ou phényle.

7. Procédé suivant l'une quelconque des revendications 1 à 6, pour la préparation d'un composé de formule (I) suivant la revendication 1 ou d'un sel de celui-ci acceptable du point de vue pharmaceutique, dans lequel n dans Z est 1 ou 2, R_{14} est un atome d'hydrogène et R_{15} est un atome d'hydrogène ou un groupe méthyle.

8. Procédé suivant l'une quelconque des revendications 1 à 7, pour la préparation d'un composé de formule (I) suivant la revendication 1 ou d'un sel de celui-ci acceptable du point de vue pharmaceutique, dans lequel n dans Z est 1.

9. Procédé suivant l'une quelconque des revendications 1 à 7, pour la préparation d'un composé de formule (I) choisi parmi les suivants:
11-amino-1,2,3,4-tétrahydro-6H-quinindolin-1-one,

11-amino-3,3-diméthyl-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
(±)-11-amino-3-phényl-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
11-amino-6-méthyl-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
11-amino-6-éthyl-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
11-amino-6-n-propyl-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
11-amino-6-(2-propényl)-1,2,3,4-tétrahydro-6H-quinindobn-1-one,
11-amino-1,2,3,4-tétrahydro-3,3,6-triméthyl-6H-quinindolin-1-one,
(±)-11-amino-6-méthyl-3-phényl-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
(±)-11-amino-3,6-diméthyl-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
(±)-11-amino-2,6-diméthyl-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
(+)-11-amino-2,6-diméthyl-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
(-)-11-amino-2,6-diméthyl-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
(±)-11-amino-2-éthyl-6-méthyl-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
11-amino-1,2,3,4-tétrahydro-2,2,6-triméthyl-6H-quinindolin-1-one,
(±)-11-amino-6-méthyl-2-(2-propynyl)-1,2,3,4-tétrahydro-6H-quinindolin-1-one,
(±)-11-amino-1,2,3,4-tétrahydro-2,4,6-triméthyl-6H-quinindolin-1-one,
12-amino-7-méthyl-cyclohepta-[5,6]-pyrido-[2,3-b]-indol-1-one,
10-amino-5-méthyl-cyclopenta-[5,6]-pyrido-[2,3-b]-indol-1-one ou
(±)-12-amino-2,7-diméthyl-cyclohepta-[5,6]-pyrido-[2,3-b]-indol-1-one,
ou un sel de l'un quelconque de ces composés acceptables du point de vue pharmaceutique.

10. Utilisation d'un composé de formule (I) suivant l'une quelconque des revendications 1 à 9, ou d'un sel de celui-ci acceptable du point de vue pharmaceutique, dans la fabrication d'un médicament pour le traitement de l'anxiété ou de la dépression chez les mammifères.

11. Procédé pour la préparation d'une composition pharmaceutique, qui comprend le mélange d'un composé de formule (I) suivant la revendication 1 ou d'un sel de celui-ci acceptable du point de vue pharmaceutique, et d'un support acceptable du point de vue pharmaceutique.